CO

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 April 2004 (22.04.2004)

PCT

(10) International Publication Number
WO 2004/033431 A2

(51) International Patent Classification[7]: C07D 231/00

(21) International Application Number:
PCT/US2003/031509

(22) International Filing Date: 2 October 2003 (02.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/416,193 4 October 2002 (04.10.2002) US
60/417,120 7 October 2002 (07.10.2002) US

(71) Applicant *(for all designated States except US)*: **ARENA PHARMACEUTICALS, INC.** [US/US]; 6166 Nancy Ridge Drive, San Diego, CA 92121-3223 (US).

(71) Applicants and
(72) Inventors: **SEMPLE, Graeme** [GB/US]; 15920 Camino Codorniz, San Diego, CA 92127 (US). **SHIN, Young, Jun** [KR/US]; 3696 Nobel Drive #268, San Diego, CA 92122 (US).

(74) Agent: **SPRUCE, Lyle**; Arena Pharmaceuticals, Inc., 6166 Nancy Ridge Drive, San Diego, CA 92121-3223 (US).

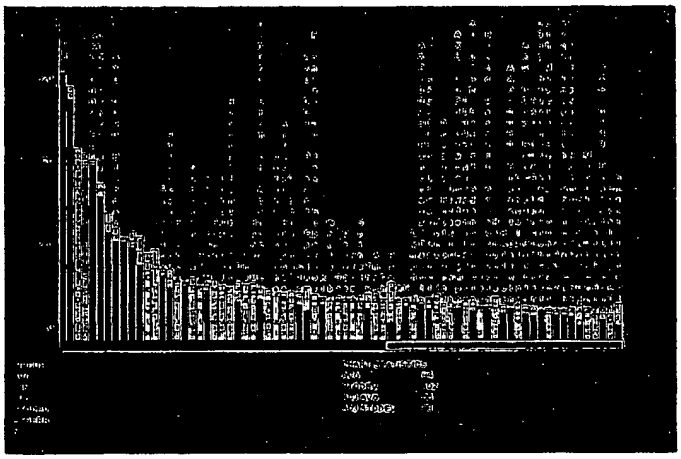
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

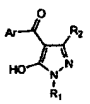
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HYDROXYPYRAZOLES AND METHODS OF PROPHYLAXIS OR TREATMENT OF METABOLIC-RELATED DISORDERS THEREOF





(I)

(57) Abstract: The present invention relates to certain hydroxypyrazole derivatives of Formula (I), and pharmaceutically acceptable salts thereof, which exhibit useful pharmaceutical properties, for example as agonists for the nicotinic acid receptor. Also provided by the present invention are pharmaceutical compositions containing compounds of the invention, and methods of using the compounds and compositions of the invention in the prophylaxis or treatment of metabolic-related disorders, including dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, type 2 diabetes, Syndrome-X and the like. In addition, the present invention also provides for the use of the compounds of the invention in combination with other active agents such as those belonging to the class of α-glucosidase inhibitors, aldose reductase inhibitors, biguanides, HMG-CoA reductase inhibitors, squalene synthesis inhibitors, fibrates, LDL catabolism enhancers, angiotensin converting enzyme (ACE) inhibitors, insulin secretion enhancers and the like.

WO 2004/033431 A2

HYDROXYPYRAZOLES AND METHODS OF PROPHYLAXIS OR TREATMENT OF METABOLIC-RELATED DISORDERS THEREOF

FIELD OF THE INVENTION

The present invention relates to certain hydroxypyrazole derivatives, and pharmaceutically acceptable salts thereof, which exhibit useful pharmaceutical properties, for example as agonists for the nicotinic acid receptor. Also provided by the present invention are pharmaceutical compositions containing compounds of the invention, and methods of using the compounds and compositions of the invention in the prophylaxis or treatment of metabolic-related disorders, including dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, type 2 diabetes, Syndrome-X and the like. In addition, the present invention also provides for the use of the compounds of the invention in combination with other active agents such as those belonging to the class of α-glucosidase inhibitors, aldose reductase inhibitors, biguanides, HMG-CoA reductase inhibitors, squalene synthesis inhibitors, fibrates, LDL catabolism enhancers, angiotensin converting enzyme (ACE) inhibitors, insulin secretion enhancers, thiazolidinedione and the like.

BACKGROUND OF THE INVENTION

A. Compounds of the invention as Antilipolytic Agents

Atherosclerosis and stroke are the numbers one and number three leading causes of death of both men and women in the United States. Type 2 diabetes is a public health problem that is serious, widespread and increasing. Elevated levels of low density lipoprotein (LDL) cholesterol or low levels of high density lipoprotein (HDL) cholesterol are, independently, risk factors for atherosclerosis and associated cardiovascular pathologies. In addition, high levels of plasma free fatty acids are associated with insulin resistance and type 2 diabetes. One strategy for decreasing LDL-cholesterol, increasing HDL-cholesterol, and decreasing plasma free fatty acids is to inhibit lipolysis in adipose tissue. This approach involves regulation of hormone sensitive lipase, which is the rate-limiting enzyme in lipolysis. Lipolytic agents increase cellular levels of cAMP, which leads to activation of hormone sensitive lipase within adipocytes. Agents that lower intracellular cAMP levels, by contrast, would be antilipolytic.

It is also worth noting in passing that an increase in cellular levels of cAMP down-regulates the secretion of adiponectin from adipocytes [Delporte, ML et al. *Biochem J* (2002) July]. Reduced levels of plasma adiponectin have been associated with metabolic-related disorders, including atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes [Matsuda, M et al. J Biol Chem (2002) July and reviewed therein].

Nicotinic acid (niacin, pyridine-3-carboxylic acid) is a water-soluble vitamin required by the human body for health, growth and reproduction; a part of the Vitamin B complex. Nicotinic

acid is also one of the oldest used drugs for the treatment of dyslipidemia. It is a valuable drug in that it favorably affects virtually all of the lipid parameters listed above [Goodman and Gilman's Pharmacological Basis of Therapeutics, editors Harmon JG and Limbird LE, Chapter 36, Mahley RW and Bersot TP (2001) pages 971-1002]. The benefits of nicotinic acid in the treatment or prevention of atherosclerotic cardiovascular disease have been documented in six major clinical trials [Guyton JR (1998) Am J Cardiol 82:18U-23U]. Nicotinic acid and related derivatives, such as, acipimox have recently been discussed [Lorenzen, A et al (2001) Molecular Pharmacology 59:349-357]. Structure and synthesis of additional analogs or derivatives of nicotinic acid are discussed throughout the Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, Tenth Edition (1983), which is incorporated herein by reference in its entirety.

Nicotinic acid and currently existing analogs thereof inhibit the production and release of free fatty acids from adipose tissue, likely via an inhibition of adenylyl cyclase, a decrease in intracellular cAMP levels, and a concomitant decrease in hormone sensitive lipase activity. Agonists that down-regulate hormone sensitive lipase activity leading to a decrease in plasma free fatty acid levels are likely to have therapeutic value. The consequence of decreasing plasma free fatty acids is two-fold. First, it will ultimately lower LDL-cholesterol and raise HDL-cholesterol levels, independent risk factors, thereby reducing the risk of mortality due to cardiovascular incidence subsequent to atheroma formation. Second, it will provide an increase in insulin sensitivity in individuals with insulin resistance or type 2 diabetes. Unfortunately, the use of nicotinic acid as a therapeutic is partially limited by a number of associated, adverse side-effects. These include flushing, free fatty acid rebound, and liver toxicity.

The rational development of novel, nicotinic acid receptor agonists that have fewer side-effects will be valuable, but to date this has been hindered by the inability to molecularly identify the nicotinic acid receptor. Furthermore, other receptors of the same class may exist on the surface of adipocytes and similarly decrease hormone sensitive lipase activity through a reduction in the level of intracellular cAMP but without the elicitation of adverse effects such as flushing, thereby representing promising novel therapeutic targets. Recent work suggests that nicotinic acid probably acts through a specific GPCR [Lorenzen A, et al. (2001) Molecular Pharmacology 59:349-357 and reviewed therein].

B. G Protein-Coupled Receptors

Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR) class. It is estimated that there are some 30,000-40,000 genes within the human genome, and of these, approximately 2% are estimated to code for GPCRs. Receptors, including GPCRs, for which the endogenous ligand has been identified, are referred to as "known" receptors, while receptors for which the endogenous ligand has not been identified are referred to as "orphan" receptors.

GPCRs represent an important area for the development of pharmaceutical products: from approximately 20 of the 100 known GPCRs, approximately 60% of all prescription pharmaceuticals have been developed. For example, in 1999, of the top 100 brand name prescription drugs, the following drugs interact with GPCRs (the primary diseases and/or disorders treated related to the drug is indicated in parentheses):

Claritin® (allergies)	Prozac® (depression)	Vasotec® (hypertension)
Paxil® (depression)	Zoloft® (depression)	Zyprexa®(psychotic disorder)
Cozaar® (hypertension)	Imitrex® (migraine)	Zantac® (reflux)
Propulsid® (reflux disease)	Risperdal® (schizophrenia)	Serevent® (asthma)
Pepcid® (reflux)	Gaster® (ulcers)	Atrovent® (bronchospasm)
Effexor® (depression)	Depakote® (epilepsy)	Cardura®(prostatic ypertrophy)
Allegra® (allergies)	Lupron® (prostate cancer)	Zoladex® (prostate cancer)
Diprivan® (anesthesia)	BuSpar® (anxiety)	Ventolin® (bronchospasm)
Hytrin® (hypertension)	Wellbutrin® (depression)	Zyrtec® (rhinitis)
Plavix® (MI/stroke)	Toprol-XL® (hypertension)	Tenormin® (angina)
Xalatan® (glaucoma)	Singulair® (asthma)	Diovan® (hypertension)
Harnal® (prostatic hyperplasia)		

(Med Ad News 1999 Data).

GPCRs share a common structural motif, having seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane (each span is identified by number, *i.e.*, transmembrane-1 (TM-1), transmembrane-2 (TM-2), *etc.*). The transmembrane helices are joined by strands of amino acids between transmembrane-2 and transmembrane-3, transmembrane-4 and transmembrane-5, and transmembrane-6 and transmembrane-7 on the exterior, or "extracellular" side, of the cell membrane (these are referred to as "extracellular" regions 1, 2 and 3 (EC-1, EC-2 and EC-3), respectively). The transmembrane helices are also joined by strands of amino acids between transmembrane-1 and transmembrane-2, transmembrane-3 and transmembrane-4, and transmembrane-5 and transmembrane-6 on the interior, or "intracellular" side, of the cell membrane (these are referred to as "intracellular" regions 1, 2 and 3 (IC-1, IC-2 and IC-3), respectively). The "carboxy" ("C") terminus of the receptor lies in the intracellular space within the cell, and the "amino" ("N") terminus of the receptor lies in the extracellular space outside of the cell.

Generally, when a ligand binds with the receptor (often referred to as "activation" of the receptor), there is a change in the conformation of the receptor that facilitates coupling between the intracellular region and an intracellular "G-protein." It has been reported that GPCRs are "promiscuous" with respect to G proteins, *i.e.*, that a GPCR can interact with more than one G protein. *See*, Kenakin, T., 43 *Life Sciences* 1095 (1988). Although other G proteins exist,

currently, Gq, Gs, Gi, Gz and Go are G proteins that have been identified. Ligand-activated GPCR coupling with the G-protein initiates a signaling cascade process (referred to as "signal transduction"). Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition. Although not wishing to be bound to theory, it is thought that the IC-3 loop as well as the carboxy terminus of the receptor interact with the G protein.

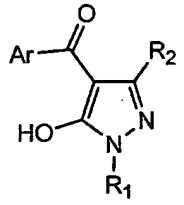
Gi-coupled GPCRs lower intracellular cAMP levels. The Melanophore technology (see *infra*) is useful for identifying Gi-coupled GPCRs.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular signaling transduction pathway to initiate signal transduction leading to a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway (via the G-protein) and produces a biological response.

A receptor may be stabilized in an active state by a ligand or a compound such as a drug. Recent discoveries, including but not exclusively limited to modifications to the amino acid sequence of the receptor, provide means other than ligands or drugs to promote and stabilize the receptor in the active state conformation. These means effectively stabilize the receptor in an active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

SUMMARY OF THE INVENTION

One aspect of the present invention encompasses novel compounds as shown in Formula (I):



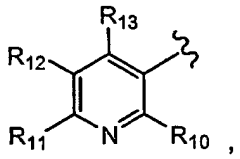
(I)

wherein:

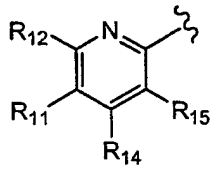
R_1 is alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, or benzyl, where the alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl or benzyl is optionally substituted with one or more halogen, hydroxy, thioxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl groups;

R_2 is H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, benzyl, phenyl or heteroaryl, where the alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, benzyl, phenyl or heteroaryl is optionally substituted with one or more halogen, hydroxy, thioxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl groups;

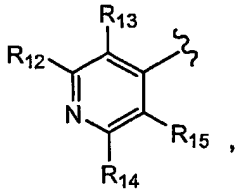
Ar is a pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl of the following formula:



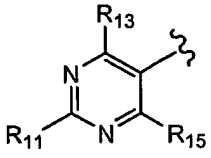
(IIa)



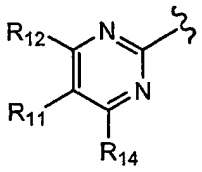
(IIb)



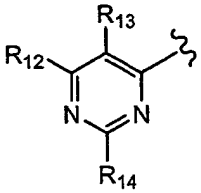
(IIc)



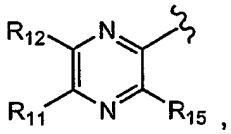
(IIIa)



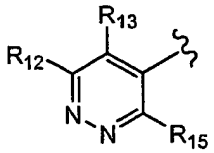
(IIIb)



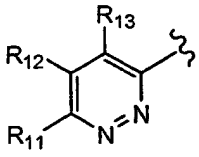
(IIIc)



(IVa)



(Va)



(Vb) ;

wherein R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently H, halogen, hydroxy, thioxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl groups; where alkyl, cycloalkyl, alkenyl, alkynyl, is optionally substituted with one or more halogen, hydroxy, thioxy, cyano, nitro, haloalkyl, amino,

aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl groups; or one or more N-oxide thereof; or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound is of Formula (I) provided that when Ar is of the Formula (IIa) then R_{11} is not C_1-C_3 haloalkyl. In one embodiment, the compound is of Formula (I) provided that when Ar is of the Formula (IIa) then R_{10} is not methyl or phenoxy; or R_{10} is not an alkyl or haloalkyl substituted with aminoalkyl, aminodialkyl, alkoxy, hydroxyl, haloalkoxy, carboalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl. In one embodiment, the compound is of Formula (I) provided that when Ar is of the Formula (IIa) then R_{12} is not halogen, haloalkyl, alkyl, alkoxy, or alkyl substituted with alkoxy.

In one embodiment, the compound is of Formula (I) provided that when Ar is of the Formula (IIb) and:

i) R_1 and R_2 are CH_3, then R_{11} is not a chlorine atom;

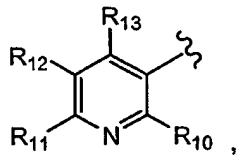
ii) R_1 and R_2 are CH_3, then R_{11} is not a bromine atom;

iii) R_1 and R_2 are CH_3, then R_{11} and R_{12} are both not chlorine atoms or both not bromine atoms;

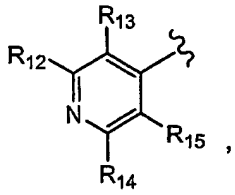
iv) R_1 and R_2 are CH_3, then R_{10}, R_{11} R_{12}, and R_{14} are not all hydrogen atoms; and

v) R_1 is CH_3, and R_2 is CF_3, then R_{11} and R_{12} are both not chlorine atoms.

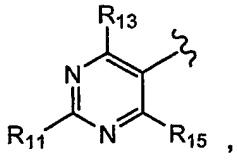
In some embodiments of the invention Ar is one of the following formulae:



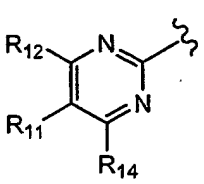
(IIa)



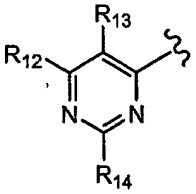
(IIc)



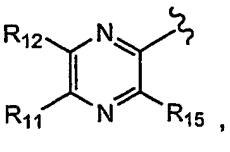
(IIIa)



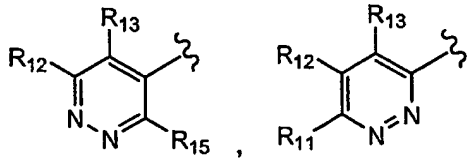
(IIIb)



(IIIc)



(IVa)



(Va) (Vb) ;

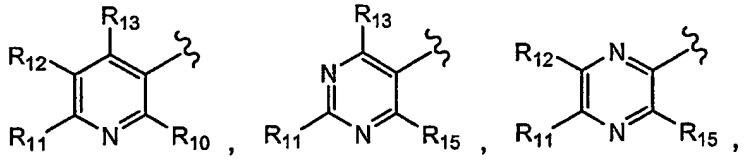
R_{10} is a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl group; and

R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl group.

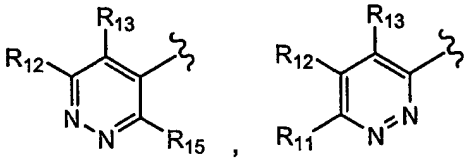
In some embodiments of the invention for when Ar is of the Formula **(IIa)**, **(IIc)**, **(IIIa)**, **(IIIb)**, **(IIIc)**, **(IVa)**, **(Va)** or **(Vb)**; R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, or alkylureyl group.

In some embodiments of the invention for when Ar is of the Formula **(IIa)**, **(IIc)**, **(IIIa)**, **(IIIb)**, **(IIIc)**, **(IVa)**, **(Va)** or **(Vb)**; R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, or alkylureyl group.

In some embodiments of the invention for when Ar is of the Formula **(IIa)**, **(IIc)**, **(IIIa)**, **(IIIb)**, **(IIIc)**, **(IVa)**, **(Va)** or **(Vb)**; R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, C_1-C_3 haloalkyl, amino, aminoalkyl, aminodialkyl, C_1-C_3 alkyl. And, in some embodiments of the invention, Ar is one of the following formulae:



(IIa) (IIIa) (IVa)



(Va) (Vb)

In some embodiments of the invention of Formula (I), R_1 is alkyl, or haloalkyl, where the alkyl or haloalkyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkoxy, haloalkoxy, alkylcarboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl or alkylureyl groups.

In some embodiments of the invention of Formula (I), R_2 is H, alkyl, haloalkyl, cycloalkyl, benzyl, phenyl or heteroaryl, where the alkyl, haloalkyl, cycloalkyl, benzyl, phenyl or heteroaryl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl or alkylureyl groups.

In some embodiments of the invention for when Ar is of the Formula (**IIa**), (**IIIa**), (**IVa**), (**Va**) or (**Vb**); R_1 is H or alkyl, where the alkyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, amino, aminoalkyl, aminodialkyl; R_2 is H, alkyl or phenyl, where the alkyl or phenyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy or haloalkoxy groups; and R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, C_1-C_3 haloalkyl, amino, aminoalkyl, aminodialkyl, C_1-C_3 alkyl.

In some embodiments of the invention of Formula (I), Ar is Formula (**IIa**); R_{11} is H, halogen, hydroxy, C_1-C_3 alkyl, or amino; and R_{10}, R_{12} and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

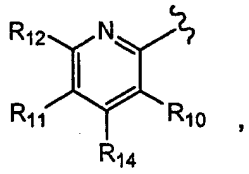
In some embodiments of the invention of Formula (I), Ar is Formula (**IIIa**); and R_{10}, R_{11}, R_{12}, and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

In some embodiments of the invention of Formula (I), Ar is Formula (**IVa**); and R_{10}, R_{11}, R_{12}, and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

In some embodiments of the invention of Formula (I), Ar is Formula (**Va**); and R_{10}, R_{11}, R_{12}, and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

In some embodiments of the invention of Formula (I), Ar is Formula (**Vb**); and R_{10}, R_{11}, R_{12}, and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

In some embodiments of the invention of Formula (I), Ar is the following formula:



(IIb)

wherein:

R_{10}, R_{11}, R_{12} and R_{14} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl group. In some embodiments, R_{10}, R_{11}, R_{12} and R_{14} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, or alkylureyl group. In some embodiments, R_{10}, R_{11}, R_{12} and R_{14} are independently a H, halogen, hydroxy, cyano, nitro, C_1-C_3 haloalkyl, amino, aminoalkyl, aminodialkyl, C_1-C_3 alkyl group. In some embodiments, R_2 is H, alkyl, haloalkyl, cycloalkyl, benzyl, phenyl or heteroaryl, where the alkyl, haloalkyl, cycloalkyl, benzyl, phenyl or heteroaryl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl or alkylureyl groups. In some embodiments R_1 is H or alkyl, where the alkyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, amino, aminoalkyl, aminodialkyl; and R_2 is H, alkyl or phenyl, where the alkyl or phenyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy or haloalkoxy groups. In some embodiments R_1 is alkyl optionally substituted with one or more halogen, hydroxy, amino, aminoalkyl, aminodialkyl. And in some embodiments R_2 is a H or alkyl, where the alkyl is optionally substituted with one or more halogen, hydroxy, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy or haloalkoxy group.

Some embodiments of the invention include compounds of the formula: (5-hydroxy-1-methyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-methyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-ethyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-isopropyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-butyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-isobutyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-neopentyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-cyclopropyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-

hydroxy-1-methyl-3-cyclopentyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-cyclohexyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-benzyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-phenyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-(3-pyridyl)-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-(2-pyridyl)-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-methyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-ethyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-propyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-isopropyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-butyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-isobutyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-neopentyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-cyclopropyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-cyclopentyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-cyclohexyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-benzyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-phenyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-(3-pyridyl)-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-(2-pyridyl)-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-(2,2,2-trifluoroethyl)-3-propyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; and (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(5-fluoro-pyridin-3-yl)-methanone.

Some embodiments of the invention include compounds of the formula: (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyridin-2-yl)-methanone; (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyrimidin-5-yl)-methanone; (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyrazin-3-yl)-methanone; (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyridazin-4-yl)-methanone; and (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyridazin-3-yl)-methanone.

In some aspects, the invention provides certain pharmaceutical compositions for treatment of metabolic-related disorders comprising compounds of Formula (I).

In further aspects, the present invention provides methods of prophylaxis or treatment of a metabolic disorder comprising the administrating to a patient in need of such administration a therapeutically or prophylactically effective amount of a compound of the invention, or a salt thereof. In some embodiments the metabolic disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes. In some embodiments the metabolic disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes.

In further aspects, the present invention provides for the use of a compound of the invention for the production of a medicament for use in prophylaxis or treatment of a metabolic

disorder. In some embodiments the metabolic disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes. In some embodiments the metabolic disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes.

In further aspects, the present invention provides a method of prophylaxis or treatment of a metabolic disorder comprising the administration to a patient in need of such treatment a therapeutically effective amount of a compound according to claim 1 in combination with one or more agent selected from the group consisting α-glucosidase inhibitor, aldose reductase inhibitor, biguanide, HMG-CoA reductase inhibitor, squalene synthesis inhibitor, fibrate, LDL catabolism enhancer, angiotensin converting enzyme inhibitor, insulin secretion enhancer and thiazolidinedione. In some embodiments the agent is a α-glucosidase inhibitor. In some embodiments the α-glucosidase inhibitor is acarbose, voglibose or miglitol. In some embodiments the α-glucosidase inhibitor is voglibose. In some embodiments the agent is an aldose reductase inhibitor. In some embodiments the aldose reductase inhibitor is tolurestat; epalrestat; imirestat; zenarestat; zopolrestat; or sorbinil. In some embodiments the agent is a biguanide. In some embodiments the biguanide is phenformin, metformin, or buformin. In some embodiments the biguanide is preferably is metformin. In some embodiments the agent is a HMG-CoA reductase inhibitor. In some embodiments the HMG-CoA reductase inhibitor is rosuvastatin, pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin. In some embodiments the agent is a fibrate. In some embodiments the fibrate is bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, or theofibrate. In some embodiments the angiotensin converting enzyme inhibitor is captopril, enalapril, alacepril, delapril; ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril or trandolapril. In some embodiments the agent is an insulin secretion enhancer. In some embodiments the insulin secretion enhancer is tolbutamide; chlorpropamide; tolazamide; acetohexamide; glycopyramide; glibenclamide; gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, glimepiride, nateglinide, or mitiglinide. In some embodiments the agent is a thiazolidinedione. In some embodiments the thiazolidinedione is rosiglitazone or pioglitazone. In some embodiments the thiazolidinedione is rosiglitazone.

These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

Applicant reserves the right to exclude any one or more of the compounds from any of the embodiments of the invention. Applicant additionally reserves the right to exclude any metabolic-related disorder or any disorder of lipid metabolism from any of the embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Figure 1 depicts a histogram representing relative expression levels of **hRUP25** detected in different human tissues *via* DNA microarray. The horizontal axis displays the different tissues, identified in vertical text above the bar. The vertical axis indicates level of expression of **hRUP25**. In Figure 1, note the high level of expression in primary adipocytes of **hRUP25**.

Figure 2. Figure 2 depicts melanophores transfected with DNA plasmids expressing **hRUP25** without treatment. These cells are pigment-aggregated because **hRUP25** are Gi-coupled receptors having a high basal level of activity, and therefore driving the aggregation to a measurable level in the absence of a ligand.

Figures 3A-B. Figures 3A and 3B illustrate the dose-dependant, nicotinic acid induced aggregation response of melanophores transfected with increasing amounts of plasmid DNA encoding **hRUP25** (Figure 3A). Cells transfected with 10μg of plasmid DNA encoding **hRUP25**, respond to nicotinic acid with an EC_{50} of about 54nM.

As negative controls, Figure 3B depicts melanophores transfected with either salmon sperm DNA (Mock) or plasmid DNA encoding the α_{2A}AR. As is evident there is no aggregation response in these cells upon nicotinic acid treatment at doses up to 10μM.

Figure 4. Figure 4 illustrates the nicotinic acid induced-inositol phosphates (IPs) accumulation in HEK293 cells co-expressing **hRUP25** and the chimeric Gαq-subunit in which the last five amino acids have been replaced with the corresponding amino acids of Gαi (GqΔGi). This construct has been shown to convert the signaling of a Gi-coupled receptor to the Gq pathway (i.e. accumulation of inositol phosphates) in response to receptor activation. Cells transfected with GqΔGi plus either empty plasmid or the constitutively activated α_{2A}AR (α_{2A}K) served as controls for the IP assay which are non-responsive to nicotinic acid.

Figures 5A-B. Figure 5A is a set of immunofluorescent photomicrographs illustrating the expression of hemaglutinin (HA)-tagged **hRUP25** in a stably transfected line of CHO cells (top; clone #46). No significant labeling is detected in mock stably-transfected CHO cells (Mock). The lower panels identify the nuclear (DAPI) staining of cells in the same field.

Figure 5B illustrates nicotinic acid and nicotine induced-inhibition of forskolin stimulated cAMP accumulation in **hRUP25**-CHO cell stable line #46(described in preceding paragraph). The EC_{50} for nicotinic acid is 23.6nM and that for nicotine is 9.8μM.

Figure 6. Figure 6 indicates that, in response to nicotinic acid, both **hRUP25** and the mouse ortholog **mRUP25** can inhibit TSHR stimulated cAMP production (in the presence and absence of TSH).

Figure 7. Figure 7 shows the saturation binding curves of [^{3}H]nicotinic acid ([^{3}H]NA) to membranes prepared from HEK293 cells transiently expressing either **hRUP25** or **mRUP25**. Note the significant binding of [^{3}H]NA relative to either that found in membranes derived from mock transfected cells or in the presence of an excess of non-labeled nicotinic acid (200μM).

Figure 8. Figure 8 is a table comparing the rank order of potency of various compounds on **hRUP25** and the pharmacologically defined nicotinic acid receptor. The potencies at **hRUP25** derived both by a functional analysis measuring the inhibition of forskolin induced cAMP production and competitive radioligand binding assays, closely match the order of potencies of the pharmacologically defined nicotinic acid receptor.

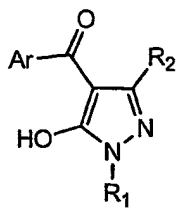
Figures 9A-B. Figure 9A depicts nicotinic acid and related compounds inhibiting isoproterenol induced lipolysis in rat epidimal fat derived adipocytes at a concentration of 10μM. P-3-T represents 3-tetrazole-5-pyridine.

Figure 9B illustrates a nicotinic acid dose-dependent inhibition of isoproterenol induced-lipolysis in rat epidimal fat derived adipocytes. Note the rightward shift in the dose-response curves with increasing concentrations of nicotinic acid.

Figure 10. Figure 10 illustrates the ability of both nicotinic acid and the related compound P-3-T (3-tetrazole-5-pyridine) to inhibit isoproterenol induced lipolysis in adipocyte primary cultures derived from human subcutaneous fat in a dose-dependant manner. The EC_{50} value for nicotinic acid and P-3-T were 716nM and 218nM respectively.

DETAILED DESCRIPTION

One aspect of the present invention encompasses novel compounds as shown in Formula (I):



(I)

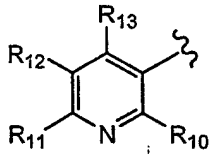
wherein:

R_1 is alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, or benzyl, where the alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl or benzyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl groups;

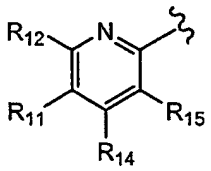
R_2 is H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, benzyl, phenyl or heteroaryl, where the alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, benzyl, phenyl or heteroaryl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl groups;

Ar is a pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl of the following formula:

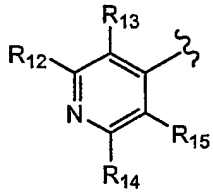
Pyridyl Ar groups:



(IIa)

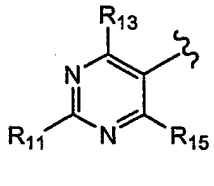


(IIb)

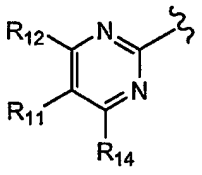


(IIc)

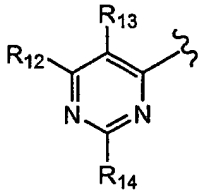
Pyrimidinyl Ar groups:



(IIIa)

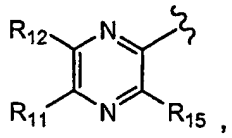


(IIIb)



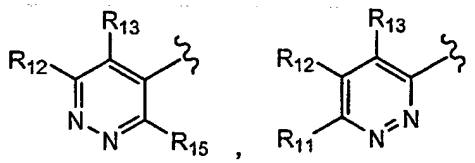
(IIIc)

Pyrazinyl Ar group:



(IVa)

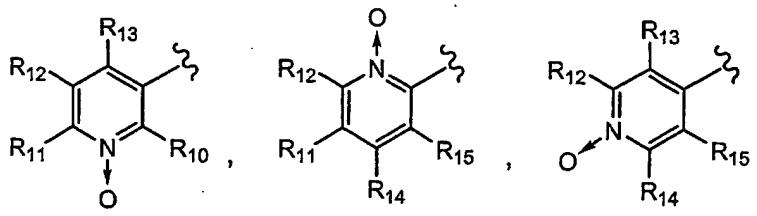
Pyridazinyl Ar groups:



(Va) **(Vb)** ;

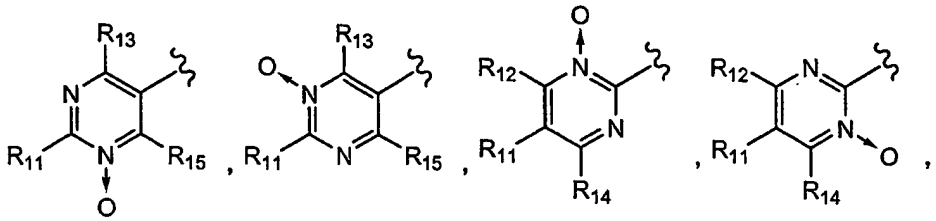
wherein R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl groups; where alkyl, cycloalkyl, alkenyl, alkynyl, is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl groups; or one or more N-oxide thereof; or a pharmaceutically acceptable salt thereof.

Some embodiments of Formula (I) include the oxidation of one or if applicable, both nitrogens prepared by using methods known in the art such as hydrogen peroxide, peracids (i.e., mCPBA) and the like. Accordingly, when Ar is a pyridyl group the aromatic ring nitrogen may be oxidized to give the representative groups as shown below in Formula **(IId)**, **(IIe)** and **(IIf)**:

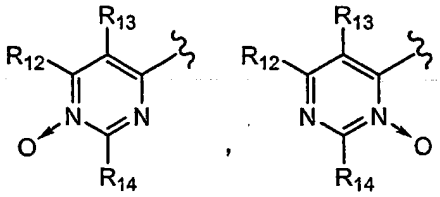


(IId) **(IIe)** **(IIf)**

When Ar is a pyrimidinyl group then one or both of the aromatic ring nitrogens may be oxidized to give the representative groups shown below in Formula **(IIId)**, **(IIIe)**, **(IIIf)**, **(IIIg)**, **(IIIh)** and **(IIIi)** (depicted below are representative examples of mono-N-oxides):

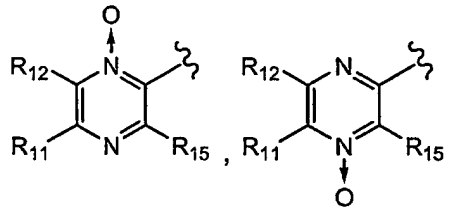


(IIId) (IIIe) (IIIf) (IIIg)



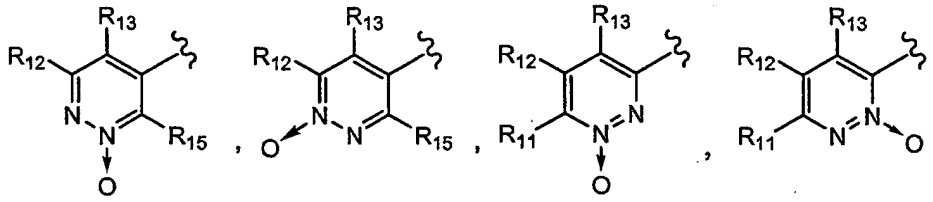
(IIIh) (IIIi)

When Ar is a pyrazinyl group then one or both of the aromatic ring nitrogens may be oxidized to give the representative groups shown below in Formula (**IVb**) and (**IVc**); (depicted below are representative examples of mono-N-oxides):



(IVb) (IVc)

When Ar is a pyridazinyl group then one or both of the aromatic ring nitrogens may be oxidized to give the representative groups shown below in Formula (**IIIc**), (**IIId**), (**IIIe**) and (**IIIf**) (depicted below are representative examples of mono-N-oxides):



(Vc) (Vd) (Ve) (Vf)

In one embodiment, the compound is of Formula (**I**) provided that when Ar is of the Formula (**IIa**) then R_{11} is not a C_1-C_3 haloalkyl, such as, CF_3, CF_2CF_3, CF_2Cl, CF_2H and CCl_3.

In one embodiment, the compound is of Formula (**I**) provided that when Ar is of the Formula (**IIa**) then R_{10} is not methyl, phenoxy, or alkyl substituted with aminoalkyl, aminodialkyl, alkoxy, haloalkoxy, carboalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl.

In one embodiment, the compound is of Formula (I) provided that when Ar is of the Formula (IIa) then R_{12} is not halogen, haloalkyl, alkyl, alkoxy, or alkyl substituted with alkoxy. In one embodiment, the compound is of Formula (I) provided that when Ar is of the Formula (IIb) and:

i) R_1 and R_2 are CH_3, then R_{11} is not a chlorine atom;

ii) R_1 and R_2 are CH_3, then R_{11} is not a bromine atom;

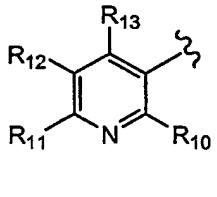
iii) R_1 and R_2 are CH_3, then R_{11} and R_{12} are both not chlorine atoms or both not bromine atoms;

v) R_1 and R_2 are CH_3, then R_{10}, R_{11} R_{12}, and R_{14} are not all hydrogen atoms; and

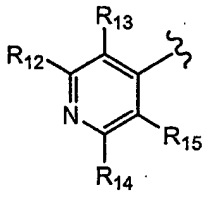
v) R_1 is CH_3, and R_2 is CF_3, then R_{11} and R_{12} are both not chlorine atoms.

In one embodiment, the compound is of Formula (I) provided that the compound is not [2-ethoxymethyl-6-(trifluoromethyl)-3-pyridinyl](5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)-methanone; 3,5-dichiloro-2-pyridinyl)5-hydroxy-1,3-dimethyl-1H-pyrazole-4-yl)-methanone; (5-bromo-2-pyridinyl)(5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)-methanone; (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)(2-phenoxy-3-pyridinyl)-methanone; (5-chloro-2-pyridinyl)(5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)-metehanone; (5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)[2-[(2-methoxyethoxy)methyl]-6-(trifluoromethyl)-3-pyridinyl]-methanone; (6-chloro-2-methyl-3-pyridinyl)(5-hydroxy-1,3-diemthyl-1H-pyrazol-4-yl)-methanone; (6-chloro-2-methyl-3-pyridinyl)(5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)-methanone; (3,5-dibromo-2-pyridinyl)(5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)-methanone; (3,5-dichloro-2-pyridinyl)[5-hydroxy-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-methanone; and (5-hydroxy-1,3,-dimethyl-1H-pyrazol-4-yl)-2-pyridinyl-methanone.

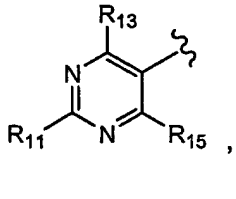
In some embodiments of the invention Ar is one of the following formulae:



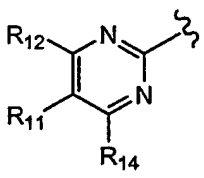
(IIa)



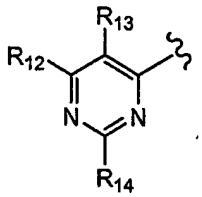
(IIc)



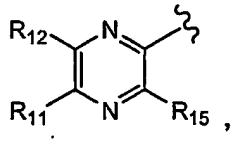
(IIIa)



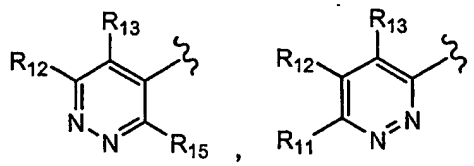
(IIIb)



(IIIc)



(IV)



(Va) (Vb) ;

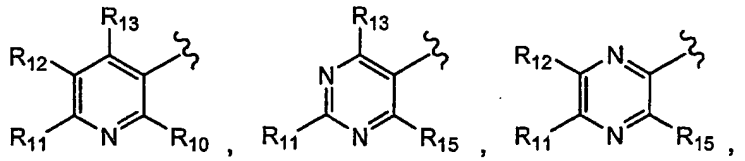
R_{10} is a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl group; and

R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl group.

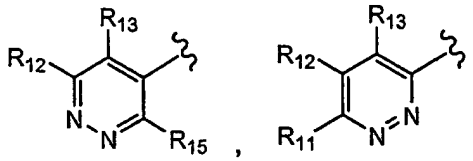
In some embodiments of the invention for when Ar is of the Formula **(IIa)**, **(IIc)**, **(IIIa)**, **(IIIb)**, **(IIIc)**, **(IVa)**, **(Va)** or **(Vb)**; R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, or alkylureyl group.

In some embodiments of the invention for when Ar is of the Formula **(IIa)**, **(IIc)**, **(IIIa)**, **(IIIb)**, **(IIIc)**, **(IVa)**, **(Va)** or **(Vb)**; R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, or alkylureyl group.

In some embodiments of the invention for when Ar is of the Formula **(IIa)**, **(IIc)**, **(IIIa)**, **(IIIb)**, **(IIIc)**, **(IVa)**, **(Va)** or **(Vb)**; R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, C_1-C_3 haloalkyl, amino, aminoalkyl, aminodialkyl, C_1-C_3 alkyl. And, in some embodiments of the invention, Ar is one of the following formulae:



(IIa) (IIIa) (IV)



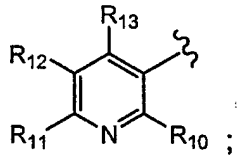
(Va) (Vb)

In some embodiments of the invention of Formula (I), R_1 is alkyl, or haloalkyl, where the alkyl or haloalkyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkoxy, haloalkoxy, alkylcarboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl or alkylureyl groups.

In some embodiments of the invention of Formula (I), R_2 is H, alkyl, haloalkyl, cycloalkyl, benzyl, phenyl or heteroaryl, where the alkyl, haloalkyl, cycloalkyl, benzyl, phenyl or heteroaryl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl or alkylureyl groups.

In some embodiments of the invention for when Ar is of the Formula (**IIa**), (**IIIa**), (**IVa**), (**Va**) or (**Vb**); R_1 is H or alkyl, where the alkyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, amino, aminoalkyl, aminodialkyl; R_2 is H, alkyl or phenyl, where the alkyl or phenyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy or haloalkoxy groups; and R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, C_1-C_3 haloalkyl, amino, aminoalkyl, aminodialkyl, C_1-C_3 alkyl.

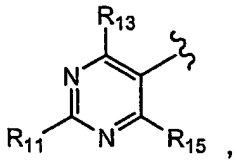
In some embodiments of the invention of Formula (I), Ar is Formula (**IIa**);



(IIa)

wherein R_{11} is H, halogen, hydroxy, C_1-C_3 alkyl, or amino; and R_{10}, R_{12} and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

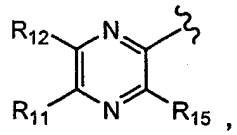
In some embodiments of the invention Ar is Formula (**IIIa**):



(IIIa)

wherein: R_{10}, R_{11}, R_{12}, and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

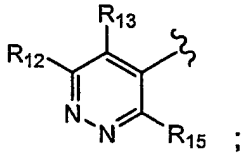
In some embodiments of the invention Ar is Formula **(IVa)**:



(IVa)

wherein R_{10}, R_{11}, R_{12}, and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

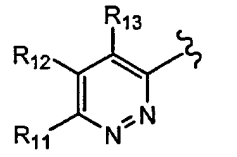
In some embodiments of the invention Ar is Formula **(Va)**:



(Va)

wherein R_{10}, R_{11}, R_{12}, and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

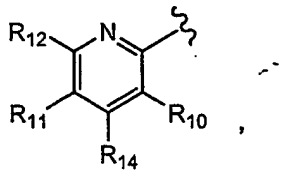
In some embodiments of the invention Ar is Formula **(Vb)**:



(Vb)

wherein R_{10}, R_{11}, R_{12}, and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

In some embodiments of the invention of Formula **(I)**, Ar is the following formula:



(IIb)

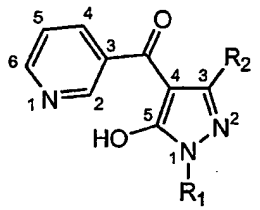
wherein:

R_{10}, R_{11}, R_{12} and R_{14} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl group. In some embodiments, R_{10}, R_{11}, R_{12} and R_{14} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, or alkylureyl group. In some embodiments, R_{10}, R_{11}, R_{12} and R_{14} are independently a H, halogen, hydroxy, cyano, nitro, C_1-C_3 haloalkyl, amino, aminoalkyl, aminodialkyl, C_1-C_3 alkyl group. In some embodiments, R_2 is H, alkyl, haloalkyl, cycloalkyl, benzyl, phenyl or heteroaryl, where the alkyl, haloalkyl, cycloalkyl, benzyl, phenyl or heteroaryl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl or alkylureyl groups. In some embodiments R_1 is H or alkyl, where the alkyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, amino, aminoalkyl, aminodialkyl; and R_2 is H, alkyl or phenyl, where the alkyl or phenyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy or haloalkoxy groups. In some embodiments R_1 is alkyl optionally substituted with one or more halogen, hydroxy, amino, aminoalkyl, aminodialkyl. And in some embodiments R_2 is a H or alkyl, where the alkyl is optionally substituted with one or more halogen, hydroxy, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy or haloalkoxy group.

In some embodiments of the invention R_1 is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $C(CH_3)_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$ $CH_2CH_2CH_2CH_2CH_3$, $CH_2CH_2CH(CH_3)_2$, $CH_2C(CH_3)_3$, $C(CH_3)_2CH_2CH_3$, $CH(CH_3)CH_2CH_2CH_3$, $CH(CH_3)CH(CH_3)_2$ or $CH_2CH_2CH_2CH_2CH_2CH_3$.

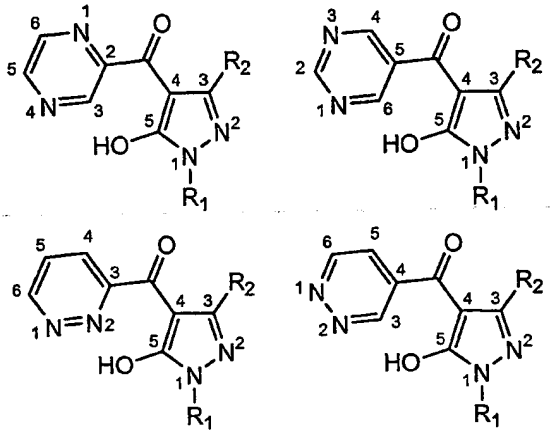
In some embodiments of the invention R_2 is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $C(CH_3)_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$ $CH_2CH_2CH_2CH_2CH_3$, $CH_2CH_2CH(CH_3)_2$, $CH_2C(CH_3)_3$, $C(CH_3)_2CH_2CH_3$, $CH(CH_3)CH_2CH_2CH_3$, $CH(CH_3)CH(CH_3)_2$ or $CH_2CH_2CH_2CH_2CH_2CH_3$.

Some embodiments of the invention include compounds of the formula: (5-hydroxy-1-methyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-methyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-ethyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-isopropyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-butyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-isobutyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-neopentyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-cyclopropyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-cyclopentyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-cyclohexyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-benzyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-phenyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-(3-pyridyl)-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-methyl-3-(2-pyridyl)-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-methyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-ethyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-propyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-isopropyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-butyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-isobutyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-neopentyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-cyclopropyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-cyclopentyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-cyclohexyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-benzyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-phenyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-(3-pyridyl)-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-ethyl-3-(2-pyridyl)-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; (5-hydroxy-1-(2,2,2-trifluoroethyl)-3-propyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; and (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(5-fluoro-pyridin-3-yl)-methanone. Wherein the numbering is based on the following structure:



Some embodiments of the invention include compounds of the formula: (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyridin-2-yl)-methanone; (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyrimidin-5-yl)-methanone; (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-

(pyrazin-3-yl)-methanone; (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyridazin-4-yl)-methanone; and (5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyridazin-3-yl)-methanone. Wherein the numbering is based on the following structure:



The invention also encompasses certain pharmaceutical compositions for treatment of metabolic-related disorders comprising compounds of Formula (I).

The invention also provides a method of prophylaxis or treatment of a metabolic disorder comprising the administrating to a patient in need of such administration a therapeutically or prophylactically effective amount of a compound of the present invention. Metabolic disorders include but are not limited to dyslipidemia, atherosclerosis, coronary heart disease, insulin resitance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes. In some embodiments the metabolic disease is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes.

In further aspects, the present invention provides a method of prophylaxis or treatment of a metabolic disorder comprising the administration to a patient in need of such treatment a therapeutically effective amount of a compound of the present invention in combination with one or more of an agent selected from the group consisting α-glucosidase inhibitor, aldose reductase inhibitor, biguanide, HMG-CoA reductase inhibitor, squalene synthesis inhibitor, fibrate, LDL catabolism enhancer, angiotensin converting enzyme inhibitor, insulin secretion enhancer and thiazolidinedione. In some embodiments the agent is a α-glucosidase inhibitor. In some embodiments the α-glucosidase inhibitor is acarbose, voglibose or miglitol. In some embodiments the α-glucosidase inhibitor is voglibose. In some embodiments the agent is an aldose reductase inhibitor. In some embodiments the aldose reductase inhibitor is tolurestat; epalrestat; imirestat; zenarestat; zopolrestat; or sorbinil. In some embodiments the agent is a biguanide. In some embodiments the biguanide is phenformin, metformin, or buformin. In some embodiments the biguanide is preferably is metformin. In some embodiments the agent is a

HMG-CoA reductase inhibitor. In some embodiments the HMG-CoA reductase inhibitor is rosuvastatin, pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin. In some embodiments the agent is a fibrate. In some embodiments the fibrate is bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, or theofibrate. In some embodiments the angiotensin converting enzyme inhibitor is captopril, enalapril, alacepril, delapril; ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril or trandolapril. In some embodiments the agent is an insulin secretion enhancer. In some embodiments the insulin secretion enhancer is tolbutamide; chlorpropamide; tolazamide; acetohexamide; glycopyramide; glibenclamide; gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, glimepiride, nateglinide, or mitiglinide. In some embodiments the agent is a thiazolidinedione. In some embodiments the thiazolidinedione is rosiglitazone or pioglitazone. In some embodiments the thiazolidinedione is rosiglitazone.

These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

Definitions

The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control:

AFFINITY REAGENTS shall mean compounds that specifically and measurably bind to a target molecule. Preferably the target molecule is a GPCR of the invention. Preferably the AFFINITY REAGENTS are labeled to facilitate detection.

AGONISTS shall mean materials (*e.g.*, ligands, candidate compounds) that activate an intracellular response when they bind to the receptor. In some embodiments, AGONISTS are those materials not previously known to activate the intracellular response when they bind to the receptor (*e.g.* to enhance GTPγS binding to membranes or to lower intracellular cAMP level). In some embodiments, AGONISTS are those materials not previously known to inhibit lipolysis when they bind to the receptor.

ALLOSTERIC MODULATORS shall mean materials (*e.g.*, ligands, candidate compounds) that affect the functional activity of the receptor but which do not inhibit the endogenous ligand from binding to the receptor. Allosteric modulators include inverse agonists, partial agonists and agonists.

AMINO ACID ABBREVIATIONS used herein are set out in Table A:

TABLE A		
ALANINE	ALA	A
ARGININE	ARG	R
ASPARAGINE	ASN	N
ASPARTIC ACID	ASP	D
CYSTEINE	CYS	C
GLUTAMIC ACID	GLU	E
GLUTAMINE	GLN	Q
GLYCINE	GLY	G
HISTIDINE	HIS	H
ISOLEUCINE	ILE	I
LEUCINE	LEU	L
LYSINE	LYS	K
METHIONINE	MET	M
PHENYLALANINE	PHE	F
PROLINE	PRO	P
SERINE	SER	S
THREONINE	THR	T
TRYPTOPHAN	TRP	W
TYROSINE	TYR	Y
VALINE	VAL	V

ANTAGONISTS shall mean materials (*e.g.*, ligands, candidate compounds) that competitively bind to the receptor at the same site as the agonists but which do not activate an intracellular response, and can thereby inhibit the intracellular responses elicited by agonists. ANTAGONISTS do not diminish the baseline intracellular response in the absence of an agonist. In some embodiments, ANTAGONISTS are those materials not previously known to compete with an agonist to inhibit the cellular response when they bind to the receptor, *e.g.* wherein the cellular response is GTPγS binding to membranes or to the lowering of intracellular cAMP level.

ANTIBODIES are intended herein to encompass monoclonal antibodies and polyclonal antibodies. ANTIBODIES are further intended to encompass IgG, IgA, IgD, IgE, and IgM. ANTIBODIES include whole antibodies, including single-chain whole antibodies, and antigen binding fragments thereof, including Fab, Fab', F(ab)2 and F(ab')2. ANTIBODIES may be from

any animal origin. Preferably, ANTIBODIES are human, murine, rabbit, goat, guinea pig, hamster, camel, donkey, sheep, horse or chicken. Preferably ANTIBODIES have binding affinities with a dissociation constant or Kd value less than $5x10^{-6}M$, $10^{-6}M$, $5x10^{-7}M$, $10^{-7}M$, $5x10^{-8}M$, $10^{-8}M$, $5x10^{-9}M$, $10^{-9}M$, $5x10^{-10}M$ $10^{-10}M$, $5x10^{-11}M$, $10^{-11}M$, $5x10^{-12}M$, $10^{-12}M$, $5x10^{-13}M$, $10^{-13}M$, $5x10^{-14}M$ $10^{-14}M$, $5x10^{-15}M$ and $10^{-15}M$. ANTIBODIES of the present invention may be prepared by any suitable method known in the art.

ANTILIPOLYTIC GPCR shall mean a GPCR expressed by adipocytes and coupled to Gi or a Gi-coupled GPCR belonging to the nicotinic acid receptor sub-family of GPCRs. Activation of a Gi-coupled GPCR on adipocytes lowers intracellular cAMP levels, resulting in an inhibition of hormone sensitive lipase activity.

ATHEROSCLEROSIS is intended herein to encompass disorders of large and medium-sized arteries that result in the progressive accumulation within the intima of smooth muscle cells and lipids.

CANDIDATE COMPOUND shall mean a molecule (for example, and not limitation, a chemical compound) that is amenable to a screening technique. Preferably, the phrase "candidate compound" does not include compounds which were publicly known to be compounds selected from the group consisting of inverse agonist, agonist or antagonist to a receptor, as previously determined by an indirect identification process ("indirectly identified compound"); more preferably, not including an indirectly identified compound which has previously been determined to have therapeutic efficacy in at least one mammal; and, most preferably, not including an indirectly identified compound which has previously been determined to have therapeutic utility in humans.

CHEMICAL GROUP, MOIETY or RESIDUE shall have the following meaing in the specification and Formulae described herein:

The term "**acyl**" denotes a radical containing 1 to 8 carbons such as formyl, acetyl, propionyl, butanoyl, *iso*-butanoyl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like.

The term "**acyloxy**" denotes a radical containing 1 to 8 carbons of an acyl group defined above directly attached to an oxygen such as acetyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy, benzoyloxy and the like.

The term "**alkenyl**" denotes a radical containing 1 to 12 carbons unless otherwise specified. Some embodiments are 1 to 10 carbons, some embodiments are 1 to 8 carbons, some embodiments are 1 to 6 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons, and some embodiments are 1 or 2 carbons. Examples of an alkenyl include vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexanyl, 2-heptenyl, 3-

heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl and the like. Furthermore, the term "**alkenyl**" includes dienes and trienes of straight and branch chains.

The term "**alkoxy**" as used herein denotes a radical alkyl, defined above, attached directly to an oxygen such as methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy and the like.

The term "**alkyl**" denotes a radical containing 1 to 12 carbons unless otherwise specified. Some embodiments are 1 to 10 carbons, some embodiments are 1 to 8 carbons, some embodiments are 1 to 6 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons, and some embodiments are 1 or 2 carbons. Examples of an alkyl include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *t*-butyl, amyl, *t*-amyl, *n*-pentyl and the like.

The term "**alkylamide**" denotes an acyl radical attached to an amine or monoalkylamine, wherein the term acyl has the same definition as found above. Examples of "alkylamide" include acetamido, propionamido and the like.

The term "**alkylcarboxamido**" denotes a single alkyl group attached to the amine of an amide, wherein alkyl has the same definition as found above. Examples include *N*-methylcarboxamide, *N*-ethylcarboxamide, *N*-(*iso*-propyl)carboxamide and the like.

The term "**alkynyl**" denotes a radical containing 1 to 12 carbons unless otherwise specified. Some embodiments are 1 to 10 carbons, some embodiments are 1 to 8 carbons, some embodiments are 1 to 6 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons, and some embodiments are 1 or 2 carbons. Example of an alkynyl include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like. The term "**alkynyl**" includes di- and tri-ynes.

The term "**alkylsulfinyl**" denotes a sulfoxide, i.e., -S(O)-, radical containing 1 to 8 carbons, linear or branched. Examples include methylsulfinyl, ethylsulfinyl and the like.

The term "**alkylsulfonyl**" denotes a sulfone, i.e., $-S(O)_2-$, radical containing 1 to 8 carbons, linear or branched. Examples include methylsulfonyl, ethylsulfonyl and the like.

The term "**alkylthio**" denotes a sulfide, i.e., -S-, radical containing 1 to 8 carbons, linear or branched. Examples include methylsulfide, ethylsulfide, isopropylsulfide and the like.

The term "**alkylureyl**" denotes the group -NC(O)N- where one are both of the nitrogens are substituted with the same or different alkyl group.

The term "**amino**" denotes the group $-NH_2$.

The term "**aminoalkyl**" denotes an amino substituted with one group selected from alkyl or arylalkyl wherein the terms have the same definitions found throughout.

The term "**aminodialkyl**" denotes an amino substituted with two radicals that may be same or different selected from aryl, substituted aryl, alkyl, substituted alkyl or arylalkyl wherein the terms have the same definitions found throughout. Some examples include dimethylamino, methylethylamino, diethylamino and the like.

The term "**aryl**" denotes an aromatic ring radical containing 6 ring carbons, also referred to as phenyl.

The term "**arylalkyl**" defines a C_1-C_4 alkylene, such as $-CH_2-$, $-CH_2CH_2-$ and the like, which is further substituted with an aryl group. Examples of an "arylalkyl" include benzyl, phenethylene and the like.

The term "**arylcarboxamido**" denotes a single aryl group attached to the amine of an amide, wherein aryl has the same definition as found above. The example is *N*-phenylcarboxamide.

The term "**arylureyl**" denotes the group -NC(O)N- where one are both of the nitrogens are substituted with an aryl.

The term "**benzyl**" denotes the group $-CH_2C_6H_6$.

The term "**carboalkoxy**" refers to an alkyl ester of a carboxylic acid, wherein alkyl has the same definition as found above. Examples include carbomethoxy, carboethoxy, carboisopropoxy and the like.

The term "**carboxy**" denotes the group $-CO_2H$; also is referred to as carboxylic acid.

The term "**cyano**" denotes the group –CN.

The term "**cycloalkyl**" denotes a ring radical containing 3 to 8 carbons, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclopenyl, cyclohexyl, cycloheptyl and the like.

The term "**dialkylcarboxamido**" denotes two alkyl or arylalkyl groups, that are the same or different, attached to the amine of an amide, wherein alkyl has the same definition as found above. Examples of a dialkylcarboxamide include *N*,*N*-dimethylcarboxamide, *N*-methyl-*N*-ethylcarboxamide and the like.

The term "**halo**" or "**halogen**" denotes to a fluoro, chloro, bromo or iodo group.

The term "**haloalkoxy**" denotes a haloalkyl, as defined above, that is directly attached to an oxygen to form a difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy and the like.

The term "**haloalkyl**" denotes a radical alkyl, defined above, substituted with one or more halogens, preferably fluorine, such as a fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and the like.

The term "**haloalkylsulfinyl**" denotes a sulfoxide, i.e., -S(O)-, radical containing 1 to 8 carbons substituted with one or more halogens, linear or branched. Examples include trifluoromethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, 2,2-difluoroethylsulfinyl and the like.

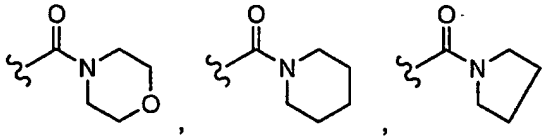
The term "**haloalkylsulfonyl**" denotes a sulfone, i.e., $-S(O)_2-$, radical containing 1 to 8 carbons, linear or branched substituted with one or more halogens. Examples include trifluoromethylsulfonyl, 2,2,2-trifluoroethylsulfonyl, 2,2-difluoroethylsulfonyl and the like.

The term "**heteroaryl**" denotes an an aryl ring wherein one or more of the ring carbons are substituted with a nitrogen, examples include, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, and the like.

The term "**heteroarylcarboxamido**" denotes a single heteroaryl group attached to the amine of an amide, wherein aryl has the same definition as found above. The example is *N*-(2-pyridyl)carboxamide, *N*-(3-pyridyl)carboxamide, *N*-(4-pyridyl)carboxamide, *N*-(2-pyrazinyl)carboxamide, *N*-(4-pyridazine)carboxamide, *N*-(5-pyrimidinyl)carboxamide, *N*-(2-pyrimidinyl)carboxamide and the like.

The term "**heterocyclic**" denotes a non-aromatic carbon ring substituted with one, two or three heteroatoms, such as, piperidinyl, morpholinyl, piperzinyl, pyrrolidinyl, and the like.

The term "**heterocycliccarboxamido**" denotes a heterocyclic group with a ring nitrogen where the ring nitrogen is bonded directly to the carbonyl forming an amide. Examples include:



and the like.

The term "**hydroxy**" denotes the group –OH.

The term "**nitro**" denotes the group $-NO_2$.

The term "**phenoxy**" denotes an aryl group attached to an oxygen atom.

The term "**thiohaloalkyl**" denotes a thioalkyl radical substituted with one or more halogens. Examples include trifluoromethylthio, 1,1-difluoroethylthio, 2,2,2-trifluoroethylthio and the like.

The term "**thioxy**" denotes the group –SH.

CODON shall mean a grouping of three nucleotides (or equivalents to nucleotides) which generally comprise a nucleoside (adenosine (A), guanosine (G), cytidine (C), uridine (U) and thymidine (T)) coupled to a phosphate group and which, when translated, encodes an amino acid.

COMPOSITION means a material comprising at least one component; a "pharmaceutical composition" is an example of a composition.

COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality; i.e. the ability to activate/inhibit a signal transduction pathway, in contrast to receptor binding affinity. Exemplary means of detecting compound efficacy are disclosed in the Example section of this patent document.

COMPRISING, CONSISTING ESSENTIALLY OF, and **CONSISTING OF** are defined herein according to their standard meaning. A defined meaning set forth in the M.P.E.P. controls over a defined meaning in the art and a defined meaning set forth in controlling Federal Circuit case law controls over a meaning set forth in the M.P.E.P.

CONSTITUTIVELY ACTIVE RECEPTOR shall mean a receptor stabilized in an active state by means other than through binding of the receptor to its ligand or a chemical equivalent thereof. A CONSTITUTIVELY ACTIVE RECEPTOR may be endogenous or non-endogenous.

CONSTITUTIVELY ACTIVATED RECEPTOR shall mean an endogenous receptor that has been modified so as to be constitutively active.

CONSTITUTIVE RECEPTOR ACTIVATION shall mean activation of a receptor in the absence of binding to its ligand or a chemical equivalent thereof.

CONTACT or **CONTACTING** shall mean bringing at least two moieties together, whether in an in vitro system or an in vivo system.

CORONARY HEART DISEASE is intended herein to encompass disorders comprising a narrowing of the small blood vessels that supply blood and oxygen to the heart. CORONARY HEART DISEASE usually results from the build up of fatty material and plaque. As the coronary arteries narrow, the flow of blood to the heart can slow or stop. CORONARY HEART DISEASE can cause chest pain (stable angina), shortness of breath, heart attack, or other symptoms.

DECREASE is used to refer to a reduction in a measurable quantity and is used synonymously with the terms "reduce", "diminish", "lower", and "lessen".

DIABETES as used herein is intended to encompass the usual diagnosis of DIABETES made from any of the methods including, but not limited to, the following list: symptoms of diabetes (*e.g.*, polyuria, polydipsia, polyphagia) plus casual plasma glucose levels of greater than or equal to 200 mg/dl, wherein casual plasma glucose is defined any time of the day regardless of the timing of meal or drink consumption; 8 hour fasting plasma glucose levels of less than or equal to 126 mg/dl; and plasma glucose levels of greater than or equal to 200 mg/dl 2 hours following oral administration of 75 g anhydrous glucose dissolved in water.

DIRECTLY IDENTIFYING or **DIRECTLY IDENTIFIED**, in relationship to the phrase "candidate compound", shall mean the screening of a candidate compound against a constitutively activated receptor, preferably a constitutively activated orphan receptor, and most preferably against a constitutively activated G protein-coupled cell surface orphan receptor, and assessing the compound efficacy of such compound. This phrase is, under no circumstances, to be interpreted or understood to be encompassed by or to encompass the phrase "indirectly identifying" or "indirectly identified."

DISORDERS OF LIPID METABOLISM are intended herein to include, but not be limited to, dyslipidemia.

DYSLIPIDEMIA is intended herein to encompass disorders comprising any one of elevated level of plasma free fatty acids, elevated level of plasma cholesterol, elevated level of LDL-cholesterol, reduced level of HDL-cholesterol, and elevated level of plasma triglycerides.

ENDOGENOUS shall mean a material that a mammal naturally produces. ENDOGENOUS in reference to, for example and not limitation, the term "receptor," shall mean that which is naturally produced by a mammal (for example, and not limitation, a human) or a virus. ENDOGENOUS shall be understood to encompass all allelic variants of a gene represented within the genome of said mammal as well as the allelic polypeptide variants so encoded. By contrast, the term **NON-ENDOGENOUS** in this context shall mean that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus. For example, and not limitation, a receptor which is not constitutively active in its endogenous form, but when manipulated becomes constitutively active, is most preferably referred to herein as a "non-endogenous, constitutively activated receptor." Both terms can be utilized to describe both "in vivo" and "in vitro" systems. For example, and not limitation, in a screening approach, the endogenous or non-endogenous receptor may be in reference to an in vitro screening system. As a further example and not limitation, where the genome of a mammal has been manipulated to include a non-endogenous constitutively activated receptor, screening of a candidate compound by means of an in vivo system is viable.

G PROTEIN COUPLED RECEPTOR FUSION PROTEIN and **GPCR FUSION PROTEIN**, in the context of the invention disclosed herein, each mean a non-endogenous

protein comprising an endogenous, constitutively activate GPCR or a non-endogenous, constitutively activated GPCR fused to at least one G protein, most preferably the alpha (α) subunit of such G protein (this being the subunit that binds GTP), with the G protein preferably being of the same type as the G protein that naturally couples with endogenous orphan GPCR. For example, and not limitation, in an endogenous state, if the G protein "$G_s\alpha$" is the predominate G protein that couples with the GPCR, a GPCR Fusion Protein based upon the specific GPCR would be a non-endogenous protein comprising the GPCR fused to $G_s\alpha$; in some circumstances, as will be set forth below, a non-predominant G protein can be fused to the GPCR. The G protein can be fused directly to the C-terminus of the constitutively active GPCR or there may be spacers between the two.

HOST CELL shall mean a cell capable of having a Plasmid and/or Vector incorporated therein. In the case of a prokaryotic Host Cell, a Plasmid is typically replicated as a autonomous molecule as the Host Cell replicates (generally, the Plasmid is thereafter isolated for introduction into a eukaryotic Host Cell); in the case of a eukaryotic Host Cell, a Plasmid is integrated into the cellular DNA of the Host Cell such that when the eukaryotic Host Cell replicates, the Plasmid replicates. In some embodiments the Host Cell is eukaryotic, more preferably, mammalian, and most preferably selected from the group consisting of 293, 293T and COS-7 cells.

IN NEED OF TREATMENT as used herein refers to a judgement made by a caregiver (e.g. physician, nurse, nurse practitioner, etc. in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from treatment. This judgement is made based on a variety of factors that are in the realm of a caregiver's expertise, but that include the knowledge that the individual or animal is ill, or will be ill, as the result of a condition that is treatable by the compounds of the invention.

INDIRECTLY IDENTIFYING or **INDIRECTLY IDENTIFIED** means the traditional approach to the drug discovery process involving identification of an endogenous ligand specific for an endogenous receptor, screening of candidate compounds against the receptor for determination of those which interfere and/or compete with the ligand-receptor interaction, and assessing the efficacy of the compound for affecting at least one second messenger pathway associated with the activated receptor.

INDIVIDUAL as used herein refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

INHIBIT or **INHIBITING**, in relationship to the term "response" shall mean that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

INSULIN RESISTANCE as used herein is intended to encompass the usual diagnosis of insulin resistance made by any of a number of methods, including but not restricted to: the intravenous glucose tolerance test or measurement of the fasting insulin level. It is well known that there is an excellent correlation between the height of the fasting insulin level and the degree of insulin resistance. Therefore, one could use elevated fasting insulin levels as a surrogate marker for insulin resistance for the purpose of identifying which normal glucose tolerance (NGT) individuals have insulin resistance. A diagnosis of insulin resistance can also be made using the euglycemic glucose clamp test.

INVERSE AGONISTS shall mean materials (*e.g.*, ligand, candidate compound) that bind either to the endogenous form or to the constitutively activated form of the receptor so as to reduce the baseline intracellular response of the receptor observed in the absence of agonists.

ISOLATED shall mean that the material is removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or DNA or polypeptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such a polynucleotide could be part of a vector and/or such a polynucleotide or polypeptide could be part of a composition, and still be isolated in that the vector or composition is not part of its natural environment.

KNOCKOUT MOUSE/RAT is intended herein to encompass a mouse or rat that has been manipulated by recombinant means such that a single gene of choice has been inactivated or "knocked-out" in a manner that leaves all other genes unaffected.

KNOWN RECEPTOR shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has been identified.

LIGAND shall mean a molecule specific for a naturally occurring receptor.

METABOLIC-RELATED DISORDERS are intended herein to include, but not be limited to, dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes.

As used herein, the terms **MODULATE** or **MODIFY** are meant to refer to an increase or decrease in the amount, quality, or effect of a particular activity, function or molecule.

MUTANT or **MUTATION** in reference to an endogenous receptor's nucleic acid and/or amino acid sequence shall mean a specified change or changes to such endogenous sequences such that a mutated form of an endogenous non-constitutively activated receptor evidences constitutive activation of the receptor. In terms of equivalents to specific sequences, a subsequent mutated form of a human receptor is considered to be equivalent to a first mutation of the human receptor if (a) the level of constitutive activation of the subsequent mutated form of a human receptor is substantially the same as that evidenced by the first mutation of the receptor;

and (b) the percent sequence (amino acid and/or nucleic acid) homology between the subsequent mutated form of the receptor and the first mutation of the receptor is at least 80%, at least 85%, at least 90%, at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, and most preferably at least 99%. In some embodiments, owing to the fact that some preferred cassettes disclosed herein for achieving constitutive activation include a single amino acid and/or codon change between the endogenous and the non-endogenous forms of the GPCR, it is preferred that the percent sequence homology should be at least 98%.

As used herein, the term **NICOTINIC ACID ANALOG OR DERIVATIVE** is meant to molecules which bind to nicotinic acid receptors and have substantially similar effects on the receptor. Such analogs and derivatives are well-known to those skilled in the art and include, but are not limited to, acipimox and niacinamide.

NON-ORPHAN RECEPTOR shall mean an endogenous naturally occurring molecule specific for an identified ligand wherein the binding of a ligand to a receptor activates an intracellular signaling pathway.

ORPHAN RECEPTOR shall mean an endogenous receptor for which the ligand specific for that receptor has not been identified or is not known.

PARTIAL AGONISTS shall mean materials (*e.g.*, ligands, candidate compounds) that activate the intracellular response when they bind to the receptor to a lesser degree/extent than do full agonists.

PHARMACEUTICAL COMPOSITION shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

PLASMID shall mean the combination of a Vector and cDNA. Generally, a Plasmid is introduced into a Host Cell for the purposes of replication and/or expression of the cDNA as a protein.

POLYNUCLEOTIDES shall mean RNA, DNA, or RNA/DNA hybrid sequences of more than one nucleotide in either single chain or duplex form. The polynucleotides of the invention may be prepared by any known method, including synthetic, recombinant, ex vivo generation, or a combination thereof, as well as utilizing any purification methods known in the art.

POLYPEPTIDE shall refer to a polymer of amino acids without regard to the length of the polymer. Thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide. This term also does not specify or exclude post-expression modifications of polypeptides. For example, polypeptides that include the covalent attachment of glycosyl

groups, acetyl groups, phosphate groups, lipid groups and the like are expressly encompassed by the term POLYPEPTIDE.

PRIMER is used herein to denote a specific oligonucleotide sequence which is complementary to a target nucleotide sequence and used to hybridize to the target nucleotide sequence. A primer serves as an initiation point for nucleotide polymerization catalyzed by DNA polymerase, RNA polymerase, or reverse transcriptase.

PURIFIED is used herein to describe a polynucleotide or polynucleotide vector of the invention that has been separated from other compounds including, but not limited to, other nucleic acids, carbohydrates, lipids and proteins (such as the enzymes used in the synthesis of the polynucleotide). A polynucleotide is substantially pure when at least about 50%, 60%, 75%, or 90% of a sample contains a single polynucleotide sequence. A substantially pure polynucleotide typically comprises about 50, 60, 70, 80, 90, 95, 99% weight/weight of a nucleic acid sample. Polynucleotide purity or homogeneity may be indicated by a number of means well known in the art, such as agarose or polyacrylamide gel electrophoresis of a sample, followed by visualizing a single polynucleotide band upon staining the gel.

Similarly, the term **PURIFIED** is used herein to describe a polypeptide of the invention that has been separated from other compounds including, but not limited to, nucleic acids, lipids, carbohydrates and other proteins. In some preferred embodiments, a polypeptide is substantially pure when at least about 50%, 60%, 75%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 99.5% of the polypeptide molecules of a sample have a single amino acid sequence. In some preferred embodiments, a substantially pure polypeptide typically comprises about 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 99.5% weight/weight of a protein sample. Polypeptide purity or homogeneity is indicated by a number of methods well known in the art, such as agarose or polyacrylamide gel electrophoresis of a sample, followed by visualizing a single polypeptide band upon staining the gel.

Further, as used herein, the term **PURIFIED** does not require absolute purity; rather, it is intended as a relative definition. Purification of starting material or natural material to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

RECEPTOR FUNCTIONALITY shall refer to the normal operation of a receptor to receive a stimulus and moderate an effect in the cell, including, but not limited to regulating gene transcription, regulating the influx or efflux of ions, effecting a catalytic reaction, and/or modulating activity through G-proteins.

SECOND MESSENGER shall mean an intracellular response produced as a result of receptor activation. A second messenger can include, for example, inositol triphosphate (IP_3), diacylglycerol (DAG), cyclic AMP (cAMP), and cyclic GMP (cGMP). Second messenger

response can be measured for a determination of receptor activation. In addition, second messenger response can be measured for the direct identification of candidate compounds, including for example, inverse agonists, partial agonists, agonists, and antagonists.

SIGNAL TO NOISE RATIO shall mean the signal generated in response to activation, amplification, or stimulation wherein the signal is above the background noise or the basal level in response to non-activation, non-amplification, or non-stimulation.

SPACER shall mean a translated number of amino acids that are located after the last codon or last amino acid of a gene, for example a GPCR of interest, but before the start codon or beginning regions of the G protein of interest, wherein the translated number amino acids are placed in-frame with the beginnings regions of the G protein of interest. The number of translated amino acids can be one, two, three, four, etc., and up to twelve.

STIMULATE or **STIMULATING**, in relationship to the term "response" shall mean that a response is increased in the presence of a compound as opposed to in the absence of the compound.

SUBJECT shall mean primates, including but not limited to humans and baboons, as well as pet animals such as dogs and cats, laboratory animals such as rats and mice, and farm animals such as horses, sheep, and cows.

SUBSTANTIALLY shall refer to a result which is within 40% of a control result, preferably within 35%, more preferably within 30%, more preferably within 25%, more preferably within 20%, more preferably within 15%, more preferably within 10%, more preferably within 5%, more preferably within 2%,and most preferably within 1% of a control result. For example, in the context of receptor functionality, a test receptor may exhibit substantially similar results to a control receptor if the transduced signal, measured using a method taught herein or similar method known to the art-skilled, is within 40% of the signal produced by a control signal.

TRANSGENIC MOUSE/RAT shall be intended herein to encompass a mouse or rat that has been engineered through recombinant means to carry a foreign gene, or transgene, of choice as part of its own genetic material.

VECTOR in reference to cDNA shall mean a circular DNA capable of incorporating at least one cDNA and capable of incorporation into a Host Cell.

The order of the following sections is set forth for presentational efficiency and is not intended, nor should be construed, as a limitation on the disclosure or the claims to follow.

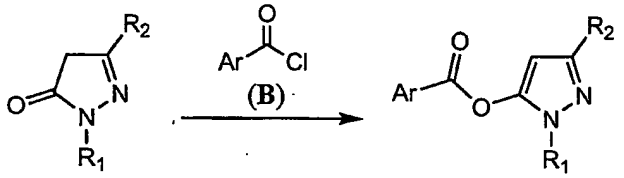
Synthetic Methods of Hydroxypyrazoles

The compounds of the present invention can be readily prepared according to a variety of synthetic regimes, all of which would be familiar to one skilled in the art. The chemical literature quotes numerous procedures for the synthesis of pyrazol-3-ones, and relevant pyridyl,

pyrimidinyl, pyrazinyl or pyridazinyl carboxylic acids and esters. Some related articles include: Katritsky and co-workers, *J. Hetrocycl. Chem.* **1993**, *30*, 135-139; Fray and co-workers, *J. Med. Chem.* **1995**, *38*, 3524-3535; Wang and co-workers, Synth. Commun. **2000**, *30*, 763-770; Butler and DeWald, *J. Org. Chem.* **1971**, *36*, 2542-2547; Duffy and co-workers, *J. Med. Chem.* **2001**, *44*, 3730-3745; Khan and co-workers, *J. Hetrocycl. Chem.* **2001**, *38*, 193-198; and Heinisch and co-workers, *J. Hetrocycl. Chem.* **1991**, *28*, 1047-1050.

In the illustrated syntheses outlined below, the labeled substituents have the same identifications as set out in the definitions of the compound described above. As shown below, the methods described thereafter may be used for the preparation of compound of Formula (I).

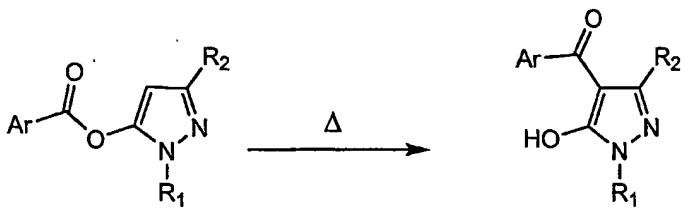
One method that may be used to prepare compounds of Formula (I) utilizes the intermediate of Formula (A). In this instance, ester (C) may be formed from an Ar-carboxylic derivative by a variety of methods. Some methods include, but are not limited to, the use of an acid halide or anhydride, the use of coupling reagents and the like. Preparations for an acid chloride from the corresponding acid are known in art. Some typical methods include: thionyl chloride, oxalyl chloride and the like. The preparation of anhydrides may be realized by the dehydration of 2 equivalents of the corresponding carboxylic acid, such as through the use DCC, and the like; or by addition of the carboxylic acid chloride to the corresponding carboxylic acid. In addition, a wide range of coupling methods are available that may be used to generate an ester, these include, but are not limited to, DCC/HOBt and the like. This process is illustrated in Reaction Scheme (1) depicting the ester forming reaction between a pyrazol-3-one (A) with an acid chloride (B) as shown below:



(A) (C)

Reaction Scheme (1)

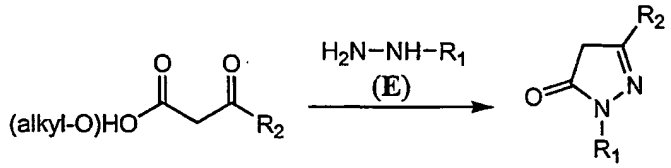
Either ester (C) can be isolated or can be rearranged with heat to compounds of Formula (I). Therefore, pyrzol-3-one can be directly converted to compounds of Formula (I) without isolation of intermediate ester (C) or pyrzaol-3-one can be transformed into ester (C) and purified, prior to the conversion to compounds of Formula (I). The process for the conversion of ester (C) is shown in Reaction Scheme (2) below:



(C) (I)

Reaction Scheme (2)

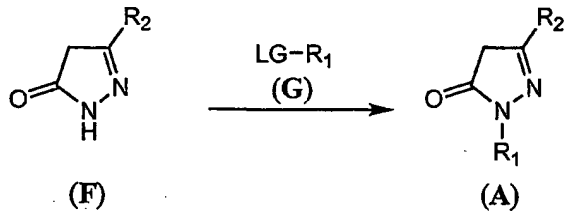
A variety of methods are available for the preparation of pyrazol-3-ones use in Reaction Scheme (1). By way of example, pyrazol-3-ones may be prepared directly from the cyclization of 2,4-ketoester or acid derivatives and subsubstituted hydrazines as depicted in Reaction Scheme (3). In this example, the R_1 and R_2 groups may be introduced into the pyrazol-3-ones by the appropriate selection of the desired hydrazine and 2,4-ketoester or acid derivative respectively. One particular feature of the 2,4-ketoester or acid derivatives is the diverse number of R_2 groups may be introduced by a variety of methods known in the art. Likewise, a wide variety of substituted hydrazines may also be prepared with many of them many being commercially available.



(D) (A)

Reaction Scheme (3)

A variety of pyrazol-3-ones can be prepared whereby the R_1 is introduced via an alkylation type reaction as shown in Reaction Scheme (4). Ultizing pyrazol-3-one (F) the R_1 group may be introduced in a similar manner as reported by Katritzky and co-workers in *J. Heterocycl. Chem.* **1993**, *30*, 135-139. This approach allows for the R_2 group to constant while introducing a variety of R_1 groups through the readily available or easily prepared alkylhalide. It is comprehended that other leaving groups (i.e., LG), such as, mesylate, tosylate, and the like, may also be used.



(F) (A)

Reaction Scheme (4)

A wide variety of compound of the invention may be prepared by the methods described above and by those known in the art. Examples of compounds of the invention are shown in the tables below:

TABLE 1-1

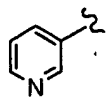
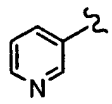
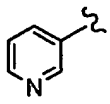
Ar	R_1	R_2
	$-CH_3$	-H
	$-CH_3$	$-CH_3$
	$-CH_3$	$-CH_2CH_3$
	$-CH_3$	$-CH_2CH_2CH_3$
	$-CH_3$	$-CH(CH_3)_2$
	$-CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_3$	$-CH_2C(CH_3)_3$
	$-CH_3$	$-C_3H_5$
	$-CH_3$	$-C_5H_9$
	$-CH_3$	$-C_6H_{11}$
	$-CH_3$	$-CH_2C_6H_6$
	$-CH_3$	$-C_6H_6$
	$-CH_3$	3-pyridyl
	$-CH_3$	2-pyridyl
	$-CH_2CH_3$	-H
	$-CH_2CH_3$	$-CH_3$
	$-CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_3$	3-pyridyl
	$-CH_2CH_3$	2-pyridyl
	$-CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_3$	2-pyridyl

TABLE 1-2

Ar	R_1	R_2
	$-CH(CH_3)_2$	-H
	$-CH(CH_3)_2$	$-CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2C(CH_3)_3$
	$-CH(CH_3)_2$	$-C_3H_5$
	$-CH(CH_3)_2$	$-C_5H_9$
	$-CH(CH_3)_2$	$-C_6H_{11}$
	$-CH(CH_3)_2$	$-CH_2C_6H_6$
	$-CH(CH_3)_2$	$-C_6H_6$
	$-CH(CH_3)_2$	3-pyridyl
	$-CH(CH_3)_2$	2-pyridyl
	$-CH_2CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_2CH_3$	2-pyridyl
	$-CH_2CF_3$	-H
	$-CH_2CF_3$	$-CH_3$
	$-CH_2CF_3$	$-CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2C(CH_3)_3$
	$-CH_2CF_3$	$-C_3H_5$
	$-CH_2CF_3$	$-C_5H_9$
	$-CH_2CF_3$	$-C_6H_{11}$
	$-CH_2CF_3$	$-CH_2C_6H_6$
	$-CH_2CF_3$	$-C_6H_6$
	$-CH_2CF_3$	3-pyridyl
	$-CH_2CF_3$	2-pyridyl

5

TABLE 1-3

Ar	R_1	R_2
	$-C_6H_6$	-H
	$-C_6H_6$	$-CH_3$
	$-C_6H_6$	$-CH_2CH_3$
	$-C_6H_6$	$-CH_2CH_2CH_3$
	$-C_6H_6$	$-CH(CH_3)_2$
	$-C_6H_6$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_6$	$-CH_2CH(CH_3)_2$
	$-C_6H_6$	$-CH_2C(CH_3)_3$
	$-C_6H_6$	$-C_3H_5$
	$-C_6H_6$	$-C_5H_9$
	$-C_6H_6$	$-C_6H_{11}$
	$-C_6H_6$	$-CH_2C_6H_6$
	$-C_6H_6$	$-C_6H_6$
	$-C_6H_6$	3-pyridyl
	$-C_6H_6$	2-pyridyl
	$-CH_2CO_2Et$	-H
	$-CH_2CO_2Et$	$-CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_3$
	$-CH_2CO_2Et$	$-CH(CH_3)_2$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CO_2H$	-H
	$-CH_2CO_2H$	$-CH_3$
	$-CH_2CO_2H$	$-CH_2CH_3$
	$-CH_2CO_2H$	$-CH_2CH_2CH_3$
	$-CH_2CO_2H$	$-CH(CH_3)_2$
	$-CH_2CO_2H$	$-CH_2CH_2CH_2CH_3$
	$-C_5H_9$	-H
	$-C_5H_9$	$-CH_3$
	$-C_5H_9$	$-CH_2CH_3$
	$-C_5H_9$	$-CH_2CH_2CH_3$
	$-C_5H_9$	$-CH(CH_3)_2$
	$-C_5H_9$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_{11}$	-H
	$-C_6H_{11}$	$-CH_3$
	$-C_6H_{11}$	$-CH_2CH_3$
	$-C_6H_{11}$	$-CH_2CH_2CH_3$
	$-C_6H_{11}$	$-CH(CH_3)_2$
	$-C_6H_{11}$	$-CH_2CH_2CH_2CH_3$
	$-CH_2C_6H_6$	-H
	$-CH_2C_6H_6$	$-CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_3$
	$-CH_2C_6H_6$	$-CH(CH_3)_2$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_2CH_3$

5

TABLE 1-4

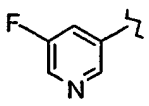
Ar	R_1	R_2
	$-CH_3$	-H
	$-CH_3$	$-CH_3$
	$-CH_3$	$-CH_2CH_3$
	$-CH_3$	$-CH_2CH_2CH_3$
	$-CH_3$	$-CH(CH_3)_2$
	$-CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_3$	$-CH_2C(CH_3)_3$
	$-CH_3$	$-C_3H_5$
	$-CH_3$	$-C_5H_9$
	$-CH_3$	$-C_6H_{11}$
	$-CH_3$	$-CH_2C_6H_6$
	$-CH_3$	$-C_6H_6$
	$-CH_3$	3-pyridyl
	$-CH_3$	2-pyridyl
	$-CH_2CH_3$	-H
	$-CH_2CH_3$	$-CH_3$
	$-CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_3$	3-pyridyl
	$-CH_2CH_3$	2-pyridyl
	$-CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_3$	2-pyridyl

TABLE 1-5

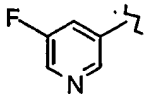
Ar	R_1	R_2
	$-CH(CH_3)_2$	-H
	$-CH(CH_3)_2$	$-CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2C(CH_3)_3$
	$-CH(CH_3)_2$	$-C_3H_5$
	$-CH(CH_3)_2$	$-C_5H_9$
	$-CH(CH_3)_2$	$-C_6H_{11}$
	$-CH(CH_3)_2$	$-CH_2C_6H_6$
	$-CH(CH_3)_2$	$-C_6H_6$
	$-CH(CH_3)_2$	3-pyridyl
	$-CH(CH_3)_2$	2-pyridyl
	$-CH_2CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_2CH_3$	2-pyridyl
	$-CH_2CF_3$	-H
	$-CH_2CF_3$	$-CH_3$
	$-CH_2CF_3$	$-CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2C(CH_3)_3$
	$-CH_2CF_3$	$-C_3H_5$
	$-CH_2CF_3$	$-C_5H_9$
	$-CH_2CF_3$	$-C_6H_{11}$
	$-CH_2CF_3$	$-CH_2C_6H_6$
	$-CH_2CF_3$	$-C_6H_6$
	$-CH_2CF_3$	3-pyridyl
	$-CH_2CF_3$	2-pyridyl

TABLE 1-6

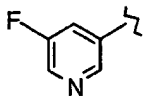
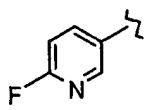
Ar	R_1	R_2
	$-C_6H_6$	-H
	$-C_6H_6$	$-CH_3$
	$-C_6H_6$	$-CH_2CH_3$
	$-C_6H_6$	$-CH_2CH_2CH_3$
	$-C_6H_6$	$-CH(CH_3)_2$
	$-C_6H_6$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_6$	$-CH_2CH(CH_3)_2$
	$-C_6H_6$	$-CH_2C(CH_3)_3$
	$-C_6H_6$	$-C_3H_5$
	$-C_6H_6$	$-C_5H_9$
	$-C_6H_6$	$-C_6H_{11}$
	$-C_6H_6$	$-CH_2C_6H_6$
	$-C_6H_6$	$-C_6H_6$
	$-C_6H_6$	3-pyridyl
	$-C_6H_6$	2-pyridyl
	$-CH_2CO_2Et$	-H
	$-CH_2CO_2Et$	$-CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_3$
	$-CH_2CO_2Et$	$-CH(CH_3)_2$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CO_2H$	-H
	$-CH_2CO_2H$	$-CH_3$
	$-CH_2CO_2H$	$-CH_2CH_3$
	$-CH_2CO_2H$	$-CH_2CH_2CH_3$
	$-CH_2CO_2H$	$-CH(CH_3)_2$
	$-CH_2CO_2H$	$-CH_2CH_2CH_2CH_3$
	$-C_5H_9$	-H
	$-C_5H_9$	$-CH_3$
	$-C_5H_9$	$-CH_2CH_3$
	$-C_5H_9$	$-CH_2CH_2CH_3$
	$-C_5H_9$	$-CH(CH_3)_2$
	$-C_5H_9$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_{11}$	-H
	$-C_6H_{11}$	$-CH_3$
	$-C_6H_{11}$	$-CH_2CH_3$
	$-C_6H_{11}$	$-CH_2CH_2CH_3$
	$-C_6H_{11}$	$-CH(CH_3)_2$
	$-C_6H_{11}$	$-CH_2CH_2CH_2CH_3$
	$-CH_2C_6H_6$	-H
	$-CH_2C_6H_6$	$-CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_3$
	$-CH_2C_6H_6$	$-CH(CH_3)_2$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_2CH_3$

TABLE 1-7

Ar	R_1	R_2
	$-CH_3$	-H
	$-CH_3$	$-CH_3$
	$-CH_3$	$-CH_2CH_3$
	$-CH_3$	$-CH_2CH_2CH_3$
	$-CH_3$	$-CH(CH_3)_2$
	$-CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_3$	$-CH_2C(CH_3)_3$
	$-CH_3$	$-C_3H_5$
	$-CH_3$	$-C_5H_9$
	$-CH_3$	$-C_6H_{11}$
	$-CH_3$	$-CH_2C_6H_6$
	$-CH_3$	$-C_6H_6$
	$-CH_3$	3-pyridyl
	$-CH_3$	2-pyridyl
	$-CH_2CH_3$	-H
	$-CH_2CH_3$	$-CH_3$
	$-CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_3$	3-pyridyl
	$-CH_2CH_3$	2-pyridyl
	$-CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_3$	2-pyridyl

5

TABLE 1-8

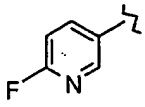
Ar	R_1	R_2
	$-CH(CH_3)_2$	-H
	$-CH(CH_3)_2$	$-CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2C(CH_3)_3$
	$-CH(CH_3)_2$	$-C_3H_5$
	$-CH(CH_3)_2$	$-C_5H_9$
	$-CH(CH_3)_2$	$-C_6H_{11}$
	$-CH(CH_3)_2$	$-CH_2C_6H_6$
	$-CH(CH_3)_2$	$-C_6H_6$
	$-CH(CH_3)_2$	3-pyridyl
	$-CH(CH_3)_2$	2-pyridyl
	$-CH_2CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_2CH_3$	2-pyridyl
	$-CH_2CF_3$	-H
	$-CH_2CF_3$	$-CH_3$
	$-CH_2CF_3$	$-CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2C(CH_3)_3$
	$-CH_2CF_3$	$-C_3H_5$
	$-CH_2CF_3$	$-C_5H_9$
	$-CH_2CF_3$	$-C_6H_{11}$
	$-CH_2CF_3$	$-CH_2C_6H_6$
	$-CH_2CF_3$	$-C_6H_6$
	$-CH_2CF_3$	3-pyridyl
	$-CH_2CF_3$	2-pyridyl

TABLE 1-9

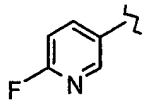
Ar	R_1	R_2
	$-C_6H_6$	-H
	$-C_6H_6$	$-CH_3$
	$-C_6H_6$	$-CH_2CH_3$
	$-C_6H_6$	$-CH_2CH_2CH_3$
	$-C_6H_6$	$-CH(CH_3)_2$
	$-C_6H_6$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_6$	$-CH_2CH(CH_3)_2$
	$-C_6H_6$	$-CH_2C(CH_3)_3$
	$-C_6H_6$	$-C_3H_5$
	$-C_6H_6$	$-C_5H_9$
	$-C_6H_6$	$-C_6H_{11}$
	$-C_6H_6$	$-CH_2C_6H_6$
	$-C_6H_6$	$-C_6H_6$
	$-C_6H_6$	3-pyridyl
	$-C_6H_6$	2-pyridyl
	$-CH_2CO_2Et$	-H
	$-CH_2CO_2Et$	$-CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_3$
	$-CH_2CO_2Et$	$-CH(CH_3)_2$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CO_2H$	-H
	$-CH_2CO_2H$	$-CH_3$
	$-CH_2CO_2H$	$-CH_2CH_3$
	$-CH_2CO_2H$	$-CH_2CH_2CH_3$
	$-CH_2CO_2H$	$-CH(CH_3)_2$
	$-CH_2CO_2H$	$-CH_2CH_2CH_2CH_3$
	$-C_5H_9$	-H
	$-C_5H_9$	$-CH_3$
	$-C_5H_9$	$-CH_2CH_3$
	$-C_5H_9$	$-CH_2CH_2CH_3$
	$-C_5H_9$	$-CH(CH_3)_2$
	$-C_5H_9$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_{11}$	-H
	$-C_6H_{11}$	$-CH_3$
	$-C_6H_{11}$	$-CH_2CH_3$
	$-C_6H_{11}$	$-CH_2CH_2CH_3$
	$-C_6H_{11}$	$-CH(CH_3)_2$
	$-C_6H_{11}$	$-CH_2CH_2CH_2CH_3$
	$-CH_2C_6H_6$	-H
	$-CH_2C_6H_6$	$-CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_3$
	$-CH_2C_6H_6$	$-CH(CH_3)_2$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_2CH_3$

TABLE 1-10

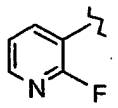
Ar	R_1	R_2
	$-CH_3$	-H
	$-CH_3$	$-CH_3$
	$-CH_3$	$-CH_2CH_3$
	$-CH_3$	$-CH_2CH_2CH_3$
	$-CH_3$	$-CH(CH_3)_2$
	$-CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_3$	$-CH_2C(CH_3)_3$
	$-CH_3$	$-C_3H_5$
	$-CH_3$	$-C_5H_9$
	$-CH_3$	$-C_6H_{11}$
	$-CH_3$	$-CH_2C_6H_6$
	$-CH_3$	$-C_6H_6$
	$-CH_3$	3-pyridyl
	$-CH_3$	2-pyridyl
	$-CH_2CH_3$	-H
	$-CH_2CH_3$	$-CH_3$
	$-CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_3$	3-pyridyl
	$-CH_2CH_3$	2-pyridyl
	$-CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_3$	2-pyridyl

TABLE 1-11

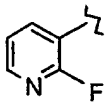
Ar	R_1	R_2
	$-CH(CH_3)_2$	-H
	$-CH(CH_3)_2$	$-CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2C(CH_3)_3$
	$-CH(CH_3)_2$	$-C_3H_5$
	$-CH(CH_3)_2$	$-C_5H_9$
	$-CH(CH_3)_2$	$-C_6H_{11}$
	$-CH(CH_3)_2$	$-CH_2C_6H_6$
	$-CH(CH_3)_2$	$-C_6H_6$
	$-CH(CH_3)_2$	3-pyridyl
	$-CH(CH_3)_2$	2-pyridyl
	$-CH_2CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_2CH_3$	2-pyridyl
	$-CH_2CF_3$	-H
	$-CH_2CF_3$	$-CH_3$
	$-CH_2CF_3$	$-CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2C(CH_3)_3$
	$-CH_2CF_3$	$-C_3H_5$
	$-CH_2CF_3$	$-C_5H_9$
	$-CH_2CF_3$	$-C_6H_{11}$
	$-CH_2CF_3$	$-CH_2C_6H_6$
	$-CH_2CF_3$	$-C_6H_6$
	$-CH_2CF_3$	3-pyridyl
	$-CH_2CF_3$	2-pyridyl

TABLE 1-12

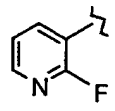
Ar	R_1	R_2
	$-C_6H_6$	-H
	$-C_6H_6$	$-CH_3$
	$-C_6H_6$	$-CH_2CH_3$
	$-C_6H_6$	$-CH_2CH_2CH_3$
	$-C_6H_6$	$-CH(CH_3)_2$
	$-C_6H_6$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_6$	$-CH_2CH(CH_3)_2$
	$-C_6H_6$	$-CH_2C(CH_3)_3$
	$-C_6H_6$	$-C_3H_5$
	$-C_6H_6$	$-C_5H_9$
	$-C_6H_6$	$-C_6H_{11}$
	$-C_6H_6$	$-CH_2C_6H_6$
	$-C_6H_6$	$-C_6H_6$
	$-C_6H_6$	3-pyridyl
	$-C_6H_6$	2-pyridyl
	$-CH_2CO_2Et$	-H
	$-CH_2CO_2Et$	$-CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_3$
	$-CH_2CO_2Et$	$-CH(CH_3)_2$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CO_2H$	-H
	$-CH_2CO_2H$	$-CH_3$
	$-CH_2CO_2H$	$-CH_2CH_3$
	$-CH_2CO_2H$	$-CH_2CH_2CH_3$
	$-CH_2CO_2H$	$-CH(CH_3)_2$
	$-CH_2CO_2H$	$-CH_2CH_2CH_2CH_3$
	$-C_5H_9$	-H
	$-C_5H_9$	$-CH_3$
	$-C_5H_9$	$-CH_2CH_3$
	$-C_5H_9$	$-CH_2CH_2CH_3$
	$-C_5H_9$	$-CH(CH_3)_2$
	$-C_5H_9$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_{11}$	-H
	$-C_6H_{11}$	$-CH_3$
	$-C_6H_{11}$	$-CH_2CH_3$
	$-C_6H_{11}$	$-CH_2CH_2CH_3$
	$-C_6H_{11}$	$-CH(CH_3)_2$
	$-C_6H_{11}$	$-CH_2CH_2CH_2CH_3$
	$-CH_2C_6H_6$	-H
	$-CH_2C_6H_6$	$-CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_3$
	$-CH_2C_6H_6$	$-CH(CH_3)_2$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_2CH_3$

TABLE 1-13

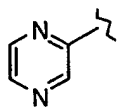
Ar	R_1	R_2
	$-CH_3$	-H
	$-CH_3$	$-CH_3$
	$-CH_3$	$-CH_2CH_3$
	$-CH_3$	$-CH_2CH_2CH_3$
	$-CH_3$	$-CH(CH_3)_2$
	$-CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_3$	$-CH_2C(CH_3)_3$
	$-CH_3$	$-C_3H_5$
	$-CH_3$	$-C_5H_9$
	$-CH_3$	$-C_6H_{11}$
	$-CH_3$	$-CH_2C_6H_6$
	$-CH_3$	$-C_6H_6$
	$-CH_3$	3-pyridyl
	$-CH_3$	2-pyridyl
	$-CH_2CH_3$	-H
	$-CH_2CH_3$	$-CH_3$
	$-CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_3$	3-pyridyl
	$-CH_2CH_3$	2-pyridyl
	$-CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_3$	2-pyridyl

TABLE 1-14

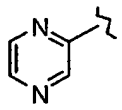
Ar	R_1	R_2
	$-CH(CH_3)_2$	-H
	$-CH(CH_3)_2$	$-CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2C(CH_3)_3$
	$-CH(CH_3)_2$	$-C_3H_5$
	$-CH(CH_3)_2$	$-C_5H_9$
	$-CH(CH_3)_2$	$-C_6H_{11}$
	$-CH(CH_3)_2$	$-CH_2C_6H_6$
	$-CH(CH_3)_2$	$-C_6H_6$
	$-CH(CH_3)_2$	3-pyridyl
	$-CH(CH_3)_2$	2-pyridyl
	$-CH_2CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_2CH_3$	2-pyridyl
	$-CH_2CF_3$	-H
	$-CH_2CF_3$	$-CH_3$
	$-CH_2CF_3$	$-CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2C(CH_3)_3$
	$-CH_2CF_3$	$-C_3H_5$
	$-CH_2CF_3$	$-C_5H_9$
	$-CH_2CF_3$	$-C_6H_{11}$
	$-CH_2CF_3$	$-CH_2C_6H_6$
	$-CH_2CF_3$	$-C_6H_6$
	$-CH_2CF_3$	3-pyridyl
	$-CH_2CF_3$	2-pyridyl

TABLE 1-15

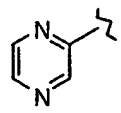
Ar	R_1	R_2
	$-C_6H_6$	-H
	$-C_6H_6$	$-CH_3$
	$-C_6H_6$	$-CH_2CH_3$
	$-C_6H_6$	$-CH_2CH_2CH_3$
	$-C_6H_6$	$-CH(CH_3)_2$
	$-C_6H_6$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_6$	$-CH_2CH(CH_3)_2$
	$-C_6H_6$	$-CH_2C(CH_3)_3$
	$-C_6H_6$	$-C_3H_5$
	$-C_6H_6$	$-C_5H_9$
	$-C_6H_6$	$-C_6H_{11}$
	$-C_6H_6$	$-CH_2C_6H_6$
	$-C_6H_6$	$-C_6H_6$
	$-C_6H_6$	3-pyridyl
	$-C_6H_6$	2-pyridyl
	$-CH_2CO_2Et$	-H
	$-CH_2CO_2Et$	$-CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_3$
	$-CH_2CO_2Et$	$-CH(CH_3)_2$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CO_2H$	-H
	$-CH_2CO_2H$	$-CH_3$
	$-CH_2CO_2H$	$-CH_2CH_3$
	$-CH_2CO_2H$	$-CH_2CH_2CH_3$
	$-CH_2CO_2H$	$-CH(CH_3)_2$
	$-CH_2CO_2H$	$-CH_2CH_2CH_2CH_3$
	$-C_5H_9$	-H
	$-C_5H_9$	$-CH_3$
	$-C_5H_9$	$-CH_2CH_3$
	$-C_5H_9$	$-CH_2CH_2CH_3$
	$-C_5H_9$	$-CH(CH_3)_2$
	$-C_5H_9$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_{11}$	-H
	$-C_6H_{11}$	$-CH_3$
	$-C_6H_{11}$	$-CH_2CH_3$
	$-C_6H_{11}$	$-CH_2CH_2CH_3$
	$-C_6H_{11}$	$-CH(CH_3)_2$
	$-C_6H_{11}$	$-CH_2CH_2CH_2CH_3$
	$-CH_2C_6H_6$	-H
	$-CH_2C_6H_6$	$-CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_3$
	$-CH_2C_6H_6$	$-CH(CH_3)_2$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_2CH_3$

TABLE 1-16

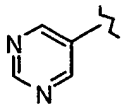
Ar	R_1	R_2
	$-CH_3$	-H
	$-CH_3$	$-CH_3$
	$-CH_3$	$-CH_2CH_3$
	$-CH_3$	$-CH_2CH_2CH_3$
	$-CH_3$	$-CH(CH_3)_2$
	$-CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_3$	$-CH_2C(CH_3)_3$
	$-CH_3$	$-C_3H_5$
	$-CH_3$	$-C_5H_9$
	$-CH_3$	$-C_6H_{11}$
	$-CH_3$	$-CH_2C_6H_6$
	$-CH_3$	$-C_6H_6$
	$-CH_3$	3-pyridyl
	$-CH_3$	2-pyridyl
	$-CH_2CH_3$	-H
	$-CH_2CH_3$	$-CH_3$
	$-CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_3$	3-pyridyl
	$-CH_2CH_3$	2-pyridyl
	$-CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_3$	2-pyridyl

TABLE 1-17

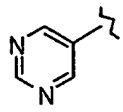
Ar	R_1	R_2
	$-CH(CH_3)_2$	-H
	$-CH(CH_3)_2$	$-CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2C(CH_3)_3$
	$-CH(CH_3)_2$	$-C_3H_5$
	$-CH(CH_3)_2$	$-C_5H_9$
	$-CH(CH_3)_2$	$-C_6H_{11}$
	$-CH(CH_3)_2$	$-CH_2C_6H_6$
	$-CH(CH_3)_2$	$-C_6H_6$
	$-CH(CH_3)_2$	3-pyridyl
	$-CH(CH_3)_2$	2-pyridyl
	$-CH_2CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_2CH_3$	2-pyridyl
	$-CH_2CF_3$	-H
	$-CH_2CF_3$	$-CH_3$
	$-CH_2CF_3$	$-CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2C(CH_3)_3$
	$-CH_2CF_3$	$-C_3H_5$
	$-CH_2CF_3$	$-C_5H_9$
	$-CH_2CF_3$	$-C_6H_{11}$
	$-CH_2CF_3$	$-CH_2C_6H_6$
	$-CH_2CF_3$	$-C_6H_6$
	$-CH_2CF_3$	3-pyridyl
	$-CH_2CF_3$	2-pyridyl

TABLE 1-18

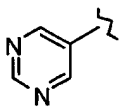
Ar	R_1	R_2
	$-C_6H_6$	-H
	$-C_6H_6$	$-CH_3$
	$-C_6H_6$	$-CH_2CH_3$
	$-C_6H_6$	$-CH_2CH_2CH_3$
	$-C_6H_6$	$-CH(CH_3)_2$
	$-C_6H_6$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_6$	$-CH_2CH(CH_3)_2$
	$-C_6H_6$	$-CH_2C(CH_3)_3$
	$-C_6H_6$	$-C_3H_5$
	$-C_6H_6$	$-C_5H_9$
	$-C_6H_6$	$-C_6H_{11}$
	$-C_6H_6$	$-CH_2C_6H_6$
	$-C_6H_6$	$-C_6H_6$
	$-C_6H_6$	3-pyridyl
	$-C_6H_6$	2-pyridyl
	$-CH_2CO_2Et$	-H
	$-CH_2CO_2Et$	$-CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_3$
	$-CH_2CO_2Et$	$-CH(CH_3)_2$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CO_2H$	-H
	$-CH_2CO_2H$	$-CH_3$
	$-CH_2CO_2H$	$-CH_2CH_3$
	$-CH_2CO_2H$	$-CH_2CH_2CH_3$
	$-CH_2CO_2H$	$-CH(CH_3)_2$
	$-CH_2CO_2H$	$-CH_2CH_2CH_2CH_3$
	$-C_5H_9$	-H
	$-C_5H_9$	$-CH_3$
	$-C_5H_9$	$-CH_2CH_3$
	$-C_5H_9$	$-CH_2CH_2CH_3$
	$-C_5H_9$	$-CH(CH_3)_2$
	$-C_5H_9$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_{11}$	-H
	$-C_6H_{11}$	$-CH_3$
	$-C_6H_{11}$	$-CH_2CH_3$
	$-C_6H_{11}$	$-CH_2CH_2CH_3$
	$-C_6H_{11}$	$-CH(CH_3)_2$
	$-C_6H_{11}$	$-CH_2CH_2CH_2CH_3$
	$-CH_2C_6H_6$	-H
	$-CH_2C_6H_6$	$-CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_3$
	$-CH_2C_6H_6$	$-CH(CH_3)_2$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_2CH_3$

TABLE 1-19

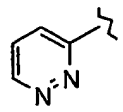
Ar	R_1	R_2
	$-CH_3$	-H
	$-CH_3$	$-CH_3$
	$-CH_3$	$-CH_2CH_3$
	$-CH_3$	$-CH_2CH_2CH_3$
	$-CH_3$	$-CH(CH_3)_2$
	$-CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_3$	$-CH_2C(CH_3)_3$
	$-CH_3$	$-C_3H_5$
	$-CH_3$	$-C_5H_9$
	$-CH_3$	$-C_6H_{11}$
	$-CH_3$	$-CH_2C_6H_6$
	$-CH_3$	$-C_6H_6$
	$-CH_3$	3-pyridyl
	$-CH_3$	2-pyridyl
	$-CH_2CH_3$	-H
	$-CH_2CH_3$	$-CH_3$
	$-CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_3$	3-pyridyl
	$-CH_2CH_3$	2-pyridyl
	$-CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_3$	2-pyridyl

TABLE 1-20

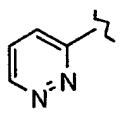
Ar	R_1	R_2
	$-CH(CH_3)_2$	-H
	$-CH(CH_3)_2$	$-CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2C(CH_3)_3$
	$-CH(CH_3)_2$	$-C_3H_5$
	$-CH(CH_3)_2$	$-C_5H_9$
	$-CH(CH_3)_2$	$-C_6H_{11}$
	$-CH(CH_3)_2$	$-CH_2C_6H_6$
	$-CH(CH_3)_2$	$-C_6H_6$
	$-CH(CH_3)_2$	3-pyridyl
	$-CH(CH_3)_2$	2-pyridyl
	$-CH_2CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_2CH_3$	2-pyridyl
	$-CH_2CF_3$	-H
	$-CH_2CF_3$	$-CH_3$
	$-CH_2CF_3$	$-CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2C(CH_3)_3$
	$-CH_2CF_3$	$-C_3H_5$
	$-CH_2CF_3$	$-C_5H_9$
	$-CH_2CF_3$	$-C_6H_{11}$
	$-CH_2CF_3$	$-CH_2C_6H_6$
	$-CH_2CF_3$	$-C_6H_6$
	$-CH_2CF_3$	3-pyridyl
	$-CH_2CF_3$	2-pyridyl

TABLE 1-21

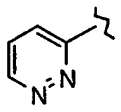
Ar	R_1	R_2
	$-C_6H_6$	-H
	$-C_6H_6$	$-CH_3$
	$-C_6H_6$	$-CH_2CH_3$
	$-C_6H_6$	$-CH_2CH_2CH_3$
	$-C_6H_6$	$-CH(CH_3)_2$
	$-C_6H_6$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_6$	$-CH_2CH(CH_3)_2$
	$-C_6H_6$	$-CH_2C(CH_3)_3$
	$-C_6H_6$	$-C_3H_5$
	$-C_6H_6$	$-C_5H_9$
	$-C_6H_6$	$-C_6H_{11}$
	$-C_6H_6$	$-CH_2C_6H_6$
	$-C_6H_6$	$-C_6H_6$
	$-C_6H_6$	3-pyridyl
	$-C_6H_6$	2-pyridyl
	$-CH_2CO_2Et$	-H
	$-CH_2CO_2Et$	$-CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_3$
	$-CH_2CO_2Et$	$-CH(CH_3)_2$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CO_2H$	-H
	$-CH_2CO_2H$	$-CH_3$
	$-CH_2CO_2H$	$-CH_2CH_3$
	$-CH_2CO_2H$	$-CH_2CH_2CH_3$
	$-CH_2CO_2H$	$-CH(CH_3)_2$
	$-CH_2CO_2H$	$-CH_2CH_2CH_2CH_3$
	$-C_5H_9$	-H
	$-C_5H_9$	$-CH_3$
	$-C_5H_9$	$-CH_2CH_3$
	$-C_5H_9$	$-CH_2CH_2CH_3$
	$-C_5H_9$	$-CH(CH_3)_2$
	$-C_5H_9$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_{11}$	-H
	$-C_6H_{11}$	$-CH_3$
	$-C_6H_{11}$	$-CH_2CH_3$
	$-C_6H_{11}$	$-CH_2CH_2CH_3$
	$-C_6H_{11}$	$-CH(CH_3)_2$
	$-C_6H_{11}$	$-CH_2CH_2CH_2CH_3$
	$-CH_2C_6H_6$	-H
	$-CH_2C_6H_6$	$-CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_3$
	$-CH_2C_6H_6$	$-CH(CH_3)_2$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_2CH_3$

TABLE 1-22

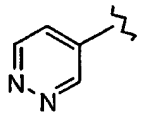
Ar	R_1	R_2
	$-CH_3$	-H
	$-CH_3$	$-CH_3$
	$-CH_3$	$-CH_2CH_3$
	$-CH_3$	$-CH_2CH_2CH_3$
	$-CH_3$	$-CH(CH_3)_2$
	$-CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_3$	$-CH_2C(CH_3)_3$
	$-CH_3$	$-C_3H_5$
	$-CH_3$	$-C_5H_9$
	$-CH_3$	$-C_6H_{11}$
	$-CH_3$	$-CH_2C_6H_6$
	$-CH_3$	$-C_6H_6$
	$-CH_3$	3-pyridyl
	$-CH_3$	2-pyridyl
	$-CH_2CH_3$	-H
	$-CH_2CH_3$	$-CH_3$
	$-CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_3$	3-pyridyl
	$-CH_2CH_3$	2-pyridyl
	$-CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_3$	2-pyridyl

TABLE 1-23

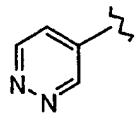
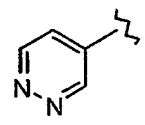
Ar	R_1	R_2
	$-CH(CH_3)_2$	-H
	$-CH(CH_3)_2$	$-CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2CH_2CH_2CH_3$
	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$
	$-CH(CH_3)_2$	$-CH_2C(CH_3)_3$
	$-CH(CH_3)_2$	$-C_3H_5$
	$-CH(CH_3)_2$	$-C_5H_9$
	$-CH(CH_3)_2$	$-C_6H_{11}$
	$-CH(CH_3)_2$	$-CH_2C_6H_6$
	$-CH(CH_3)_2$	$-C_6H_6$
	$-CH(CH_3)_2$	3-pyridyl
	$-CH(CH_3)_2$	2-pyridyl
	$-CH_2CH_2CH_2CH_3$	-H
	$-CH_2CH_2CH_2CH_3$	$-CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CH_2CH_2CH_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_3$
	$-CH_2CH_2CH_2CH_3$	$-C_3H_5$
	$-CH_2CH_2CH_2CH_3$	$-C_5H_9$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_{11}$
	$-CH_2CH_2CH_2CH_3$	$-CH_2C_6H_6$
	$-CH_2CH_2CH_2CH_3$	$-C_6H_6$
	$-CH_2CH_2CH_2CH_3$	3-pyridyl
	$-CH_2CH_2CH_2CH_3$	2-pyridyl
	$-CH_2CF_3$	-H
	$-CH_2CF_3$	$-CH_3$
	$-CH_2CF_3$	$-CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CF_3$	$-CH_2CH(CH_3)_2$
	$-CH_2CF_3$	$-CH_2C(CH_3)_3$
	$-CH_2CF_3$	$-C_3H_5$
	$-CH_2CF_3$	$-C_5H_9$
	$-CH_2CF_3$	$-C_6H_{11}$
	$-CH_2CF_3$	$-CH_2C_6H_6$
	$-CH_2CF_3$	$-C_6H_6$
	$-CH_2CF_3$	3-pyridyl
	$-CH_2CF_3$	2-pyridyl

TABLE 1-24

Ar	R_1	R_2
	$-C_6H_6$	-H
	$-C_6H_6$	$-CH_3$
	$-C_6H_6$	$-CH_2CH_3$
	$-C_6H_6$	$-CH_2CH_2CH_3$
	$-C_6H_6$	$-CH(CH_3)_2$
	$-C_6H_6$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_6$	$-CH_2CH(CH_3)_2$
	$-C_6H_6$	$-CH_2C(CH_3)_3$
	$-C_6H_6$	$-C_3H_5$
	$-C_6H_6$	$-C_5H_9$
	$-C_6H_6$	$-C_6H_{11}$
	$-C_6H_6$	$-CH_2C_6H_6$
	$-C_6H_6$	$-C_6H_6$
	$-C_6H_6$	3-pyridyl
	$-C_6H_6$	2-pyridyl
	$-CH_2CO_2Et$	-H
	$-CH_2CO_2Et$	$-CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_3$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_3$
	$-CH_2CO_2Et$	$-CH(CH_3)_2$
	$-CH_2CO_2Et$	$-CH_2CH_2CH_2CH_3$
	$-CH_2CO_2H$	-H
	$-CH_2CO_2H$	$-CH_3$
	$-CH_2CO_2H$	$-CH_2CH_3$
	$-CH_2CO_2H$	$-CH_2CH_2CH_3$
	$-CH_2CO_2H$	$-CH(CH_3)_2$
	$-CH_2CO_2H$	$-CH_2CH_2CH_2CH_3$
	$-C_5H_9$	-H
	$-C_5H_9$	$-CH_3$
	$-C_5H_9$	$-CH_2CH_3$
	$-C_5H_9$	$-CH_2CH_2CH_3$
	$-C_5H_9$	$-CH(CH_3)_2$
	$-C_5H_9$	$-CH_2CH_2CH_2CH_3$
	$-C_6H_{11}$	-H
	$-C_6H_{11}$	$-CH_3$
	$-C_6H_{11}$	$-CH_2CH_3$
	$-C_6H_{11}$	$-CH_2CH_2CH_3$
	$-C_6H_{11}$	$-CH(CH_3)_2$
	$-C_6H_{11}$	$-CH_2CH_2CH_2CH_3$
	$-CH_2C_6H_6$	-H
	$-CH_2C_6H_6$	$-CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_3$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_3$
	$-CH_2C_6H_6$	$-CH(CH_3)_2$
	$-CH_2C_6H_6$	$-CH_2CH_2CH_2CH_3$

I. Pharmaceutical compositions

Candidate compounds selected for further development can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers are available to those in the art; for example, see Remington's Pharmaceutical Sciences, 16th Edition, 1980, Mack Publishing Co., (Oslo et al., eds.).

While it is possible that, for use in the prophylaxis or treatment, a compound of the invention may in an alternative use be administered as a raw or pure chemical, it is preferable however to present the compound or active ingredient as a pharmaceutical formulation or composition.

The invention thus further provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefor and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not overly deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The dose when using the compounds of the Formula (I) can vary within wide limits, and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the Formula (I). The daily dose can be divided, especially when relatively large amounts are administered, into several, for

example 2, 3 or 4, part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose as indicated.

The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate *in vivo* data obtained in a model system, typically an animal model, to another, such as a human. Typically, animal models include, but are not limited to, the rodents diabetes models as described in Example 18, *infra*, or the mouse artherosclerosis model as described in Example 19, *infra*. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the Formula (I) and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4, part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted to the desire shape and size.

The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may contain from 0.5 to about 90 percent of the active compound; however, an artisan would know when amounts outside of this range are necessary. Suitable carriers for powders and tablets are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and

isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or

multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the compounds of the Formula (I) or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation, this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the Formula (I) as an aerosol can be prepared by processes well-known to the person skilled in the art. For their preparation, for example, solutions or dispersions of the compounds of the Formula (I) in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others, and, if appropriate, customary propellants, for example include carbon dioxide, CFC's, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane; and the like. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient may be employed.

Alternatively the active ingredients may be provided in the form of a dry powder, for example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference.

J. Combination Therapy/Prophylaxis

While the compounds of the invention can be administered as the sole active pharmaceutical agent as described herein above, they can also be used in combination with one or more agent belonging to the class of drugs known as α-glucosidase inhibitors, aldose reductase inhibitors, biguanides, HMG-CoA reductase inhibitors, squalene synthesis inhibitors, fibrate compounds, LDL catabolism enhancers and angiotensin converting enzyme (ACE) inhibitors.

α-Glucosidase inhibitors belong to the class of drugs which competitively inhibit digestive enzymes such as α-amylase, maltase, α-dextrinase, sucrase, etc. in the pancreas and or small intesting. The reversible inhibition by α-glucosidase inhibitors retard, diminish or otherwise reduce blood glucose levels by delaying the digestion of starch and sugars. Some representative examples of α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, and α-glucosidase inhibitors known in the art.

The class of aldose reductase inhibitors are drugs which inhibit the first-stage rate-limiting enzyme in the polyol pathway that prevent or arrest diabetic complications. In the hyperglycemic state of diabetes, the utilization of glucose in the polyol pathway is increased and the excess sorbitol accumulated intracellularly as a consequence acts as a tissue toxin and hence evokes the onset of complications such as diabetic neuropathy, retinopathy, and nephropathy. Examples of the aldose reductase inhibitors include tolurestat; epalrestat; 3,4-dihydro-2,8-diisopropyl-3-thioxo-2*H*-1,4-benzoxazine-4-acetic acid; 2,7-difluorospiro(9*H*-fluorene-9,4'-imidazolidine)-2',5'-dione (generic name: imirestat); 3-[(4-bromo-2-flurophenyl)methy]-7-chloro-3,4-dihydro-2,4-dioxo-1(2*H*)-quinazoline acetic acid (generic name: zenarestat); 6-fluoro-2,3-dihydro-2',5'-dioxo-spiro[4*H*-1-benzopyran-4,4'-imidazolidine]-2-carboxamide (SNK-860); zopolrestat; sorbinil; and 1-[(3-bromo-2-benzofuranyl)sulfonyl]-2,4-imidazolidinedione (M-16209), and aldose reductase inhibitors known in the art.

The biguanides are a class of drugs that stimulate anaerobic glycolysis, increase the sensitivity to insulin in the peripheral tissues, inhibit glucose absorption from the intestine, suppress of hepatic gluconeogenesis, and inhibit fatty acid oxidation. Examples of biguanides include phenformin, metformin, buformin, and biguanides known in the art.

Statin compounds belong to a class of drugs that lower blood cholesterol levels by inhibiting hydroxymethylglutalyl CoA (HMG-CoA) reductase. HMG-CoA reductase is the rate-limiting enzyme in cholesterol biosynthesis. A statin that inhibits this reductase lowers serum LDL concentrations by upregulating the activity of LDL receptors and responsible for clearing LDL from the blood. Examples of the statin compounds include rosuvastatin, pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, cerivastatin, and HMG-CoA reductase inhibitors known in the art.

Squalene synthesis inhibitors belong to a class of drugs that lower blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (S)-α-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494) and squalene synthesis inhibitors known in the art.

Fibrate compounds belong to a class of drugs that lower blood cholesterol levels by inhibiting synthesis and secretion of triglycerides in the liver and activating a lipoprotein lipase. Fibrates have been known to activate peroxisome proliferators-activated receptors and induce lipoprotein lipase expression. Examples of fibrate compounds include bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, and fibrates known in the art.

LDL (low-density lipoprotein) catabolism enhancers belong to a class of drugs that lower blood cholesterol levels by increasing the number of LDL (low-density lipoprotein) receptors, examples include LDL catabolism enhancers known in the art.

Angiotensin converting enzyme (ACE) inhibitors belong to the class of drugs that partially lower blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes. Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril; ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, and angiotensin converting enzyme inhibitors known in the art.

Insulin secretion enhancers belong to the class of drugs having the property to promote secretion of insulin from pancreatic β cells. Examples of the insulin secretion enhancers include sulfonylureas (SU). The sulfonylureas (SU) are drugs which promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in the cell membranes. Examples of the sulfonylureas include tolbutamide; chlorpropamide; tolazamide;

acetohexamide; 4-chloro-N-[(1-pyrolidinylamino) carbonyl]-benzenesulfonamide (generic name: glycopyramide) or its ammonium salt; glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, glimepiride, and other insulin secretion enhancers known in the art. Other insulin secretion enhancers include N-[[4-(1-methylethyl)cyclohexyl)carbonyl]-D-phenylalanine (Nateglinide); calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionate dihydrate (Mitiglinide, KAD-1229); and other insulin secretion enhancers known in the art.

Thiazolidinediones belong to the class of drugs more commoningly known as TZDs. Examples of thiazolidinediones include rosiglitazone, pioglitazone, and thiazolidinediones known in the art.

Some embodiments of the invention include, a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with at least one member selected from the group consisting of an α-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a HMG-CoA reductase inhibitor, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor. In another embodiment, the pharmaceutical composition is a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with a HMG-CoA reductase inhibitor. In still another embodiment, the HMG-CoA reductase inhibitor is selected from the group consisting of prevastatin, simvastatin, lovastatin, atorvastatin, fluvastatin and lipitor.

In accordance with the present invention, the combination can be used by mixing the respective active components either all together or independently with a physiologically acceptable carrier, excipient, binder, diluent, etc., as described herein above, and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When a compound or a mixture of compounds of Formula (I) are administered as a combination therapy or prophylaxis with another active compound the therapeutic agents can be formulated as a separate pharmaceutical compositions given at the same time or at different times, or the therapeutic agents can be given as a single composition.

K. Other Utility

Although a preferred use of the non-endogenous versions of the GPCRs disclosed herein may be for the direct identification of candidate compounds as inverse agonists or agonists (preferably for use as pharmaceutical agents), other uses of these versions of GPCRs exist. For example, *in vitro* and *in vivo* systems incorporating GPCRs can be utilized to further elucidate and understand the roles these receptors play in the human condition, both normal and diseased, as well as understanding the role of constitutive activation as it applies to understanding the signaling cascade. In some embodiments it is preferred that the endogenous receptors be "orphan

receptors", *i.e.*, the endogenous ligand for the receptor has not been identified. In some embodiments, therefore, the modified, non-endogenous GPCRs can be used to understand the role of endogenous receptors in the human body before the endogenous ligand has been identified. Such receptors can be used to further elucidate known receptors and the pathways through which they transduce a signal. The present methods may also be useful in developing treatment regimens for diseases and disorders associated with the tissues in which the receptors are localized. Examples of such diseases and disorders and tissues in which the receptors are localized are set forth *supra* and *infra*.

Agents that modulate (*i.e.*, increase, decrease, or block) nicotinic acid receptor functionality may be identified by contacting a candidate compound with a nicotinic acid receptor and determining the effect of the candidate compound on nicotinic acid receptor functionality. The selectivity of a compound that modulates the functionality of the nicotinic acid receptor can be evaluated by comparing its effects on the nicotinic acid receptor to its effects on other receptors. Following identification of compounds that modulate nicotinic acid receptor functionality, such candidate compounds may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity. Modulators of nicotinic acid receptor functionality will be therapeutically useful in treatment of diseases and physiological conditions in which normal or aberrant nicotinic acid receptor functionality is involved.

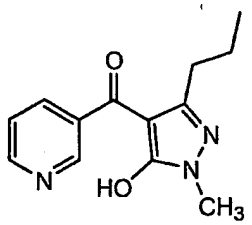
Other uses of the disclosed receptors and methods will become apparent to those in the art based upon, *inter alia*, a review of this patent document.

EXAMPLES

The following Examples are provided for illustrative purposes and not as a means of limitation. One of ordinary skill in the art would be able to design equivalent assays and methods based on the disclosure herein, all of which form part of the present invention.

Example 1

Synthesis of (5-Hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; also referred to as Compound 1 herein.

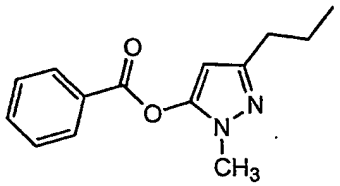


Nicotinyl chloride (3.0 g, 17.16 mmol) was dissolved in dioxan (10 mL) at room temperature and 2-Methyl-5-propyl-2,4-dihydro-pyrazol-3-one (2g, 14.3 mmol) and Calcium

hydroxide (4eq) added. The mixture was heated at 90°C with stirring, for 2h. The reaction mixture was concentrated and taken up in DMSO and purified by preparative hplc (eluting with a gradient of 0.5% TFA in acetonitrile into 0.5%TFA in water) to provide the trifluoroacetate salt of the title compound as a colorless solid following freeze drying of the product containing fractions. (hplc-ms, 5 minute gradient of 0.5% TFA in acetonitrile into 0.5%TFA in water, product eluting at ~2.1min, $(M+H)^+$=246. ^{1}H Nmr δ 0.6 (3H, t, J=7.5Hz), 1.22 (2H, m), 2.04 (2H, m) 3.10 (3H, s), 7.38 (1H, m), 7.78 (1H,m), 8.57 (2H, m) ppm).

Example 2

Synthesis of Nicotinic acid 2-methyl-5-propyl-2H-pyrazol-3-yl ester.



Nicotinyl chloride (3.0g, 17.16 mmol) was dissolved in dioxan (10 mL) at room temperature and 2-Methyl-5-propyl-2,4-dihydro-pyrazol-3-one (2g, 14.3 mmol) and Calcium hydroxide (4eq) added. The mixture was stirred at r.t. for 30 min. The solids were removed by filtration and the dioxan removed by evaporation. The resultant residue was purified by flash chromatography (eluant 1/2 v/v EtOAc/hexane) to provide the title compound as a colorless solid. (hplc-ms, 5 minute gradient of 0.5% TFA in acetonitrile into 0.5%TFA in water, product eluting at ~3.85min, $(M+H)^+$=246. ^{1}H Nmr δ 0.9 (3H, t, J=7.5Hz), 1.6 (2H, m), 2.41 (2H, m) 3.62 (3H, s), 6.03 (1H,s) 7.62 (1H, m), 8.42 (1H, m), 8.88 (1H, m) 9.13 (1H,s) ppm).

Example 3

A. Full Length Cloning

hRUP25 (Seq. Id. Nos. 1 & 2)

The disclosed human **hRUP25** was identified based upon the use of the GenBank database information. While searching the database, a cDNA clone with Accession Number AC026331 was identified as a human genomic sequence from chromosome 12. The full length **hRUP25** was cloned by PCR using primers:

5'-GCTGGAGCATTCACTAGGCGAG-3' (SEQ.ID.NO.:3; sense, 5'of initiation codon),

5'-AGATCCTGGTTCTTGGTGACAATG-3' (SEQ.ID.NO.:4; antisense, 3' of stop codon)

and human genomic DNA (Promega) as template. Advantage cDNA polymerase mix (Clontech) was used for the amplification with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 94°C for 1 minute; 94°C for 15 seconds; 56°C for 20 seconds 72°C for 1 minute 30 seconds and 72°C for 5 minutes.

A 1.2kb PCR fragment was isolated from a 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator Kit (P.E. Biosystems). *See*, SEQ.ID.NO.:1 for nucleic acid sequence and SEQ.ID.NO.:2 for deduced amino acid sequence.

B. ENDOGENOUS MOUSE AND RAT GPCRS

1. Identification of Mouse and Rat GPCRs

The mouse and rat orthologs of **hRUP25** have been identified and are disclosed below as determined from genomic sequence (see TABLE B).

TABLE B

Disclosed Mouse (m) and Rat (r) GPCRs	Accession Number Identified	Complete DNA Sequence (Base Pairs)	Open Reading Frame (Base Pairs)	Nucleic Acid SEQ.ID. NO.	Amino Acid SEQ.ID. NO.
mRU25	AJ300199	-	1,083bp	5	6
rRUP25	None	-	1,086bp	7	8

2. FULL LENGTH CLONING

a. mRUP25 (Seq. Id. Nos. 5 & 6)

In order to clone the open reading frame encoding the mouse RUP25 receptor we applied a PCR based cloning strategy. Primers were designed and synthesized based on the start and stop codon sequence of the mouse PUMA-g sequence, published on Genbank, and used on mouse genomic DNA (Promega). The PCR primers were as follows:

5'– ATGAGCAAGTCAGACCATTTTCTAGTGATA -3' (SEQ. ID. NO.:9; sense)

5'– TTATCTGGCTTCCACATCTCGTTAA –3' (SEQ. ID. NO.:10; antisense)

Advantage cDNA polymerase mix (Clontech) was used for the amplification with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 94°C for 1 minute; 94°C for 15 seconds; 56°C for 20 seconds 72°C for 1 minute 30 seconds and 72°C for 5 minutes.

A 1.2kb PCR fragment was isolated from a 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator Kit (P.E. Biosystems). *See*, SEQ.ID.NO.:1 for nucleic acid sequence and SEQ.ID.NO.:2 for deduced amino acid sequence.

b. rRUP25 (Seq. Id. Nos. 7 & 8)

The rat RUP25 receptor was cloned in an analogous fashion, however this was done assuming the sequence would be similar to the mouse sequence because there is no previously published rat sequence. Again, we applied a PCR based cloning strategy. Primers were designed and synthesized based on the start and stop codon sequence of the mouse PUMA-g

sequence, published on Genbank, and used on rat genomic DNA (Promega). The PCR primers were as follows:

5'– ATGAGCAAGTCAGACCATTTTCTAGTGATA -3' (SEQ. ID. NO.:11; sense)

5' – TTATCTGGCTTCCACATCTCGTTAA – 3' (SEQ. ID. NO.:12; antisense)

Cloned Pfu polymerase was used for the amplification by the following cycle with step 2 to 4 repeated 35 times: 94°C for 1 minute; 94°C for 30sec; 55°C for 1min; 72°C for 2min; and a final extension at 72°C for 10 minutes.

A 1.2kb PCR fragment was isolated from a 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and 12 clones were completely sequenced using the ABI Big Dye Terminator Kit (P.E. Biosystems).

Example 4

PREPARATION OF NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED GPCRS

Those skilled in the art are credited with the ability to select techniques for mutation of a nucleic acid sequence. Presented below are approaches utilized to create non-endogenous versions of several of the human GPCRs disclosed above. The mutations disclosed below are based upon an algorithmic approach whereby the 16th amino acid (located in the IC3 region of the GPCR) from a conserved proline (or an endogenous, conservative substitution therefore) residue (located in the TM6 region of the GPCR, near the TM6/IC3 interface) is mutated, preferably to an alanine, histimine, arginine or lysine amino acid residue, most preferably to a lysine amino acid residue.

Transformer Site-Directed ™ Mutagenesis

Preparation of non-endogenous human GPCRs may be accomplished on human GPCRs using, *inter alia,* Transformer Site-Directed™ Mutagenesis Kit (Clontech) according to the manufacturer instructions. Two mutagenesis primers are utilized, most preferably a lysine mutagenesis oligonucleotide that creates the lysine mutation, and a selection marker oligonucleotide. A specific example of a constituteively activated GPCR is hRUP25 and is obtained by a mutation of I230K.

Example 5

RECEPTOR EXPRESSION

Although a variety of cells are available to the art for the expression of proteins, it is most preferred that mammalian cells be utilized. The primary reason for this is predicated upon practicalities, *i.e.,* utilization of, *e.g.,* yeast cells for the expression of a GPCR, while possible, introduces into the protocol a non-mammalian cell which may not (indeed, in the case of yeast, does not) include the receptor-coupling, genetic-mechanism and secretary pathways that have evolved for mammalian systems – thus, results obtained in non-mammalian cells, while of potential use, are not as preferred as that obtained from

mammalian cells. Of the mammalian cells, COS-7, 293 and 293T cells are particularly preferred, although the specific mammalian cell utilized can be predicated upon the particular needs of the artisan.

a. Transient Transfection

On day one, $6x10^6$/ 10 cm dish of 293 cells well were plated out. On day two, two reaction tubes were prepared (the proportions to follow for each tube are per plate): tube A was prepared by mixing 4μg DNA (*e.g.*, pCMV vector; pCMV vector with receptor cDNA, etc.) in 0.5 ml serum free DMEM (Gibco BRL); tube B was prepared by mixing 24μl lipofectamine (Gibco BRL) in 0.5ml serum free DMEM. Tubes A and B were admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture". Plated 293 cells were washed with 1XPBS, followed by addition of 5 ml serum free DMEM. 1 ml of the transfection mixture were added to the cells, followed by incubation for 4hrs at 37°C/5% CO_2. The transfection mixture was removed by aspiration, followed by the addition of 10ml of DMEM/10% Fetal Bovine Serum. Cells were incubated at 37°C/5% CO_2. After 48hr incubation, cells were harvested and utilized for analysis.

b. Stable Cell Lines: Gs Fusion Protein

Approximately $12x10^6$ 293 cells are plated on a 15cm tissue culture plate. Grown in DME High Glucose Medium containing ten percent fetal bovine serum and one percent sodium pyruvate, L-glutamine, and anti-biotics. Twenty-four hours following plating of 293 cells (or to ~80% confluency), the cells are transfected using 12μg of DNA. The 12μg of DNA is combined with 60μl of lipofectamine and 2mL of DME High Glucose Medium without serum. The medium is aspirated from the plates and the cells are washed once with medium without serum. The DNA, lipofectamine, and medium mixture are added to the plate along with 10mL of medium without serum. Following incubation at 37 degrees Celsius for four to five hours, the medium is aspirated and 25ml of medium containing serum is added. Twenty-four hours following transfection, the medium is aspirated again, and fresh medium with serum is added. Forty-eight hours following transfection, the medium is aspirated and medium with serum is added containing geneticin (G418 drug) at a final concentration of 500μg/mL. The transfected cells now undergo selection for positively transfected cells containing the G418 resistant gene. The medium is replaced every four to five days as selection occurs. During selection, cells are grown to create stable pools, or split for stable clonal selection.

Example 6

ASSAYS FOR DETERMINATION OF CONSTITUTIVE ACTIVITY OF NON-ENDOGENOUS GPCRS

A variety of approaches are available for assessment of constitutive activity of the non-endogenous human GPCRs. The following are illustrative; those of ordinary skill in the art are credited with the ability to determine those techniques that are preferentially beneficial for the needs of the artisan.

1. Membrane Binding Assays: [^{35}S]GTPγS Assay

When a G protein-coupled receptor is in its active state, either as a result of ligand binding or constitutive activation, the receptor couples to a G protein and stimulates the release of GDP and subsequent binding of GTP to the G protein. The alpha subunit of the G protein-receptor complex acts as a GTPase and slowly hydrolyzes the GTP to GDP, at which point the receptor normally is deactivated. Constitutively activated receptors continue to exchange GDP for GTP. The non-hydrolyzable GTP analog, [^{35}S]GTPγS, can be utilized to demonstrate enhanced binding of [^{35}S]GTPγS to membranes expressing constitutively activated receptors. The advantage of using [^{35}S]GTPγS binding to measure constitutive activation is that: (a) it is generically applicable to all G protein-coupled receptors; (b) it is proximal at the membrane surface making it less likely to pick-up molecules which affect the intracellular cascade.

The assay utilizes the ability of G protein coupled receptors to stimulate [^{35}S]GTPγS binding to membranes expressing the relevant receptors. The assay can, therefore, be used in the direct identification method to screen candidate compounds to known, orphan and constitutively activated G protein-coupled receptors. The assay is generic and has application to drug discovery at all G protein-coupled receptors.

The [^{35}S]GTPγS assay was incubated in 20 mM HEPES and between 1 and about 20mM $MgCl_2$ (this amount can be adjusted for optimization of results, although 20mM is preferred) pH 7.4, binding buffer with between about 0.3 and about 1.2 nM [^{35}S]GTPγS (this amount can be adjusted for optimization of results, although 1.2 is preferred) and 12.5 to 75 μg membrane protein (*e.g,* 293 cells expressing the Gs Fusion Protein; this amount can be adjusted for optimization) and 10 μM GDP (this amount can be changed for optimization) for 1 hour. Wheatgerm agglutinin beads (25 μl; Amersham) were then added and the mixture incubated for another 30 minutes at room temperature. The tubes were then centrifuged at 1500 x g for 5 minutes at room temperature and then counted in a scintillation counter.

2. Adenylyl Cyclase

A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) designed for cell-based assays can be modified for use with crude plasma membranes. The Flash

Plate wells can contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in whole cells that express the receptors.

Transfected cells were harvested approximately twenty four hours after transient transfection. Media is carefully aspirated off and discarded. 10ml of PBS is gently added to each dish of cells followed by careful aspiration. 1ml of Sigma cell dissociation buffer and 3ml of PBS are added to each plate. Cells were pipetted off the plate and the cell suspension was collected into a 50ml conical centrifuge tube. Cells were then centrifuged at room temperature at 1,100 rpm for 5 min. The cell pellet was carefully re-suspended into an appropriate volume of PBS (about 3ml/plate). The cells were then counted using a hemocytometer and additional PBS was added to give the appropriate number of cells (with a final volume of about 50 µl/well).

cAMP standards and Detection Buffer [comprising 1 µCi of tracer ^{125}I-cAMP (50 µl) to 11 ml Detection Buffer] was prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer was prepared fresh for screening and contained 50µl of Stimulation Buffer, 3ul of test compound (12µM final assay concentration) and 50µl cells, Assay Buffer was stored on ice until utilized. The assay was initiated by addition of 50µl of cAMP standards to appropriate wells followed by addition of 50ul of PBSA to wells H-11 and H12. 50µl of Stimulation Buffer was added to all wells. DMSO (or selected candidate compounds) was added to appropriate wells using a pin tool capable of dispensing 3µl of compound solution, with a final assay concentration of 12µM test compound and 100µl total assay volume. The cells were then added to the wells and incubated for 60 min at room temperature. 100µl of Detection Mix containing tracer cAMP was then added to the wells. Plates were then incubated additional 2 hours followed by counting in a Wallac MicroBeta scintillation counter. Values of cAMP/well were then extrapolated from a standard cAMP curve which was contained within each assay plate.

3. Cell-Based cAMP for Gi Coupled Target GPCRs

TSHR is a Gs coupled GPCR that causes the accumulation of cAMP upon activation. TSHR will be constitutively activated by mutating amino acid residue 623 (*i.e.*, changing an alanine residue to an isoleucine residue). A Gi coupled receptor is expected to inhibit adenylyl cyclase, and, therefore, decrease the level of cAMP production, which can make assessment of cAMP levels challenging. An effective technique for measuring the decrease in production of cAMP as an indication of constitutive activation of a Gi coupled receptor can be accomplished by co-transfecting, most preferably, non-endogenous, constitutively activated TSHR (TSHR-A623I) (or an endogenous, constitutively active Gs coupled receptor) as a "signal enhancer" with

a Gi linked target GPCR to establish a baseline level of cAMP. Upon creating a non-endogenous version of the Gi coupled receptor, this non-endogenous version of the target GPCR is then co-transfected with the signal enhancer, and it is this material that can be used for screening. We will utilize such approach to effectively generate a signal when a cAMP assay is used; this approach is preferably used in the direct identification of candidate compounds against Gi coupled receptors. It is noted that for a Gi coupled GPCR, when this approach is used, an inverse agonist of the target GPCR will increase the cAMP signal and an agonist will decrease the cAMP signal.

On day one, $2X10^4$ 293 cells/well will be plated out. On day two, two reaction tubes will be prepared (the proportions to follow for each tube are per plate): tube A will be prepared by mixing 2μg DNA of each receptor transfected into the mammalian cells, for a total of 4μg DNA (*e.g.*, pCMV vector; pCMV vector with mutated THSR (TSHR-A623I); TSHR-A623I and GPCR, etc.) in 1.2ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B will be prepared by mixing 120μl lipofectamine (Gibco BRL) in 1.2ml serum free DMEM. Tubes A and B will then be admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture". Plated 293 cells will be washed with 1XPBS, followed by addition of 10ml serum free DMEM. 2.4ml of the transfection mixture will then be added to the cells, followed by incubation for 4hrs at 37°C/5% CO_2. The transfection mixture will then be removed by aspiration, followed by the addition of 25ml of DMEM/10% Fetal Bovine Serum. Cells will then be incubated at 37°C/5% CO_2. After 24hr incubation, cells will then be harvested and utilized for analysis.

A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) is designed for cell-based assays, however, can be modified for use with crude plasma membranes depending on the need of the skilled artisan. The Flash Plate wells will contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in whole cells that express the receptors.

Transfected cells will be harvested approximately twenty four hours after transient transfection. Media will be carefully aspirated off and discarded. 10ml of PBS will be gently added to each dish of cells followed by careful aspiration. 1ml of Sigma cell dissociation buffer and 3ml of PBS will be added to each plate. Cells will be pipetted off the plate and the cell suspension will be collected into a 50ml conical centrifuge tube. Cells will then be centrifuged at room temperature at 1,100 rpm for 5 min. The cell pellet will be carefully re-suspended into an appropriate volume of PBS (about 3ml/plate). The cells will then be counted using a

hemocytometer and additional PBS is added to give the appropriate number of cells (with a final volume of about 50µl/well).

cAMP standards and Detection Buffer [comprising 1 µCi of tracer ^{125}I-cAMP (50 µl) to 11 ml Detection Buffer] will be prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer should be prepared fresh for screening and contained 50µl of Stimulation Buffer, 3µl of test compound (12µM final assay concentration) and 50µl cells, Assay Buffer can be stored on ice until utilized. The assay can be initiated by addition of 50µl of cAMP standards to appropriate wells followed by addition of 50µl of PBSA to wells H-11 and H12. Fifty µl of Stimulation Buffer will be added to all wells. Selected compounds (*e.g.*, TSH) will be added to appropriate wells using a pin tool capable of dispensing 3µl of compound solution, with a final assay concentration of 12µM test compound and 100µl total assay volume. The cells will then be added to the wells and incubated for 60 min at room temperature. 100µl of Detection Mix containing tracer cAMP will then be added to the wells. Plates were then incubated additional 2 hours followed by counting in a Wallac MicroBeta scintillation counter. Values of cAMP/well will then be extrapolated from a standard cAMP curve which is contained within each assay plate.

Example 7

TISSUE DISTRIBUTION OF THE DISCLOSED HUMAN GPCRS

A. RT-PCR

RT-PCR was applied to confirm the expression and to determine the tissue distribution of several novel human GPCRs. Oligonucleotides utilized were GPCR-specific and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) were utilized for the amplification in a 40µl reaction according to the manufacturer's instructions. 20µl of the reaction will be loaded on a 1.5% agarose gel to analyze the RT-PCR products. Table C below lists the receptors, the cycle conditions and the primers utilized.

TABLE C

Receptor Identifier	Cycle Conditions Min ('), Sec (") Cycles 2-4 repeated 30 times	5' Primer (SEQ.ID.NO.)	3' Primer (SEQ.ID.NO.)	DNA Fragment	Tissue Expression
hRUP25	96° for 2' 96° for 30" 55°C for 1'	CTGATGGA CAACTATG TGAGGCGT TGG (13)	GCTGAAGC TGCTGCACA AATTTGCAC C (14)	297bp	Adipocyte, spleen, leukocyte, kidney, lung,

Receptor Identifier	Cycle Conditions Min (‘), Sec (“) Cycles 2-4 repeated 30 times	5’ Primer (SEQ.ID.NO.)	3’ Primer (SEQ.ID.NO.)	DNA Fragment	Tissue Expression
	72° for 2’ 72° for 10’				testis

Diseases and disorders related to receptors located in these tissues or regions include, but are not limited to, cardiac disorders and diseases (e.g. thrombosis, myocardial infarction; atherosclerosis; cardiomyopathies); kidney disease/disorders (e.g., renal failure; renal tubular acidosis; renal glycosuria; nephrogenic type 2 diabetes insipidus; cystinuria; polycystic kidney disease); eosinophilia; leukocytosis; leukopenia; ovarian cancer; sexual dysfunction; polycystic ovarian syndrome; pancreatitis and pancreatic cancer; irritable bowel syndrome; colon cancer; Crohn's disease; ulcerative colitis; diverticulitis; Chronic Obstructive Pulmonary Disease (COPD); Cystic Fibrosis; pneumonia; pulmonary hypertension; tuberculosis and lung cancer; Parkinson's disease; movement disorders and ataxias; learning and memory disorders; eating disorders (e.g., anorexia; bulimia, etc.); obesity; cancers; thymoma; myasthenia gravis; circulatory disorders; prostate cancer; prostatitis; kidney disease/disorders(e.g., renal failure; renal tubular acidosis; renal glycosuria; nephrogenic type 2 diabetes insipidus; cystinuria; polycystic kidney disease); sensorimotor processing and arousal disorders; obsessive-compulsive disorders; testicular cancer; priapism; prostatitis; hernia; endocrine disorders; sexual dysfunction; allergies; depression; psychotic disorders; migraine; reflux; schizophrenia; ulcers; bronchospasm; epilepsy; prostatic hypertrophy; anxiety; rhinitis; angina; and glaucoma. Accordingly, the methods of the present invention may also be useful in the diagnosis and/or treatment of these and other diseases and disorders.

B. AFFYMETRIX GENECHIP® TECHNOLOGY

Amino acid sequences were submitted to Affymetrix for the designing and manufacturing of microarray containing oligonucleotides to monitor the expression levels of G protein-coupled receptors (GPCRs) using their GeneChip® Technology. Also present on the microaccray were probes for characterized human brain tissues from Harvard Brain Band or obtained from commercially available sources. RNA samples were amplified, labeled, hybridized to the microarray, and data analyzed according to manufacturer’s instructions.

Adipose tissues were monitored for the level of gene expression of each of the GPCRs represented on the microarray. GPCRs were determined to be expressed if the expression index

was greater than 100 (based upon and according to manufacturer's instructions). The data was analyzed and had indicated that classification of GPCRs with an expression index greater than 100 was reasonable because a number of known GPCRs had previously been reported to be expressed in neuronal tissues with an expression index greater than 100.

Using the GeneChip, we discovered **hRUP25** to have high levels of expression in adipocytes suggesting that, for example, that **hRUP25** may play a role in lipolysis (*see*, Goodman & Gilman's, The Pharmacological Basis of Therapeutics, 9th Edition, page 235 (1996). *See* Figure 1. Figure 1 is a plot representing the expression level of **hRUP25** in various tissues. Based upon this data, **hRUP25** is highly expressed by primary adipocytes.

This patent document discloses the identification of nicotinic acid as a ligand and agonist of human, mouse and rat **RUP25**. *See*, Examples *infra*.

Example 8

Protocol: Direct Identification of Inverse Agonists and Agonists

A. [^{35}S]GTPγS Assay

Although we have utilized endogenous, constitutively active GPCRs for the direct identification of candidate compounds as, *e.g.*, inverse agonists, for reasons that are not altogether understood, intra-assay variation can become exacerbated. In some embodiments, a GPCR Fusion Protein, as disclosed above, is also utilized with a non-endogenous, constitutively activated GPCR. When such a protein is used, intra-assay variation appears to be substantially stabilized, whereby an effective signal-to-noise ratio is obtained. This has the beneficial result of allowing for a more robust identification of candidate compounds. Thus, in some embodiments it is preferred that for direct identification, a GPCR Fusion Protein be used and that when utilized, the following assay protocols be utilized.

1. Membrane Preparation

In some embodiments membranes comprising the constitutively active orphan GPCR/Fusion Protein of interest and for use in the direct identification of candidate compounds as inverse agonists or agonists are preferably prepared as follows:

a. Materials

"Membrane Scrape Buffer" is comprised of 20mM HEPES and 10mM EDTA, pH 7.4; "Membrane Wash Buffer" is comprised of 20 mM HEPES and 0.1 mM EDTA, pH 7.4; "Binding Buffer" is comprised of 20mM HEPES, 100 mM NaCl, and 10 mM $MgCl_2$, pH 7.4

b. Procedure

All materials will be kept on ice throughout the procedure. Firstly, the media will be aspirated from a confluent monolayer of cells, followed by rinse with 10ml cold PBS, followed by aspiration. Thereafter, 5ml of Membrane Scrape Buffer will be added to scrape cells; this will be followed by transfer of cellular extract into 50ml centrifuge tubes (centrifuged at 20,000 rpm

for 17 minutes at 4°C). Thereafter, the supernatant will be aspirated and the pellet will be resuspended in 30ml Membrane Wash Buffer followed by centrifuge at 20,000 rpm for 17 minutes at 4°C. The supernatant will then be aspirated and the pellet resuspended in Binding Buffer. This will then be homogenized using a Brinkman Polytron™ homogenizer (15-20 second bursts until the all material is in suspension). This is referred to herein as "Membrane Protein".

2. Bradford Protein Assay

Following the homogenization, protein concentration of the membranes will be determined using the Bradford Protein Assay (protein can be diluted to about 1.5mg/ml, aliquoted and frozen (-80°C) for later use; when frozen, protocol for use will be as follows: on the day of the assay, frozen Membrane Protein is thawed at room temperature, followed by vortex and then homogenized with a Polytron at about 12 x 1,000 rpm for about 5-10 seconds; it was noted that for multiple preparations, the homogenizor should be thoroughly cleaned between homogenization of different preparations).

a. Materials

Binding Buffer (as per above); Bradford Dye Reagent; Bradford Protein Standard will be utilized, following manufacturer instructions (Biorad, cat. no. 500-0006).

b. Procedure

Duplicate tubes will be prepared, one including the membrane, and one as a control "blank". Each contained 800µl Binding Buffer. Thereafter, 10µl of Bradford Protein Standard (1mg/ml) will be added to each tube, and 10µl of membrane Protein will then be added to just one tube (not the blank). Thereafter, 200µl of Bradford Dye Reagent will be added to each tube, followed by vortex of each. After five (5) minutes, the tubes will be re-vortexed and the material therein will be transferred to cuvettes. The cuvettes will then be read using a CECIL 3041 spectrophotometer, at wavelength 595.

3. Direct Identification Assay

a. Materials

GDP Buffer consisted of 37.5 ml Binding Buffer and 2mg GDP (Sigma, cat. no. G-7127), followed by a series of dilutions in Binding Buffer to obtain 0.2 µM GDP (final concentration of GDP in each well was 0.1 µM GDP); each well comprising a candidate compound, has a final volume of 200µl consisting of 100µl GDP Buffer (final concentration, 0.1µM GDP), 50µl Membrane Protein in Binding Buffer, and 50µl [^{35}S]GTPγS (0.6 nM) in Binding Buffer (2.5 µl [^{35}S]GTPγS per 10ml Binding Buffer).

b. Procedure

Candidate compounds will be preferably screened using a 96-well plate format (these can be frozen at -80°C). Membrane Protein (or membranes with expression vector excluding the GPCR Fusion Protein, as control), will be homogenized briefly until in suspension. Protein concentration will then be determined using the Bradford Protein Assay set forth above. Membrane Protein (and control) will then be diluted to 0.25mg/ml in Binding Buffer (final assay concentration, 12.5µg/well). Thereafter, 100 µl GDP Buffer was added to each well of a Wallac Scintistrip™ (Wallac). A 5ul pin-tool will then be used to transfer 5 µl of a candidate compound into such well (*i.e.*, 5µl in total assay volume of 200 µl is a 1:40 ratio such that the final screening concentration of the candidate compound is 10µM). Again, to avoid contamination, after each transfer step the pin tool should be rinsed in three reservoirs comprising water (1X), ethanol (1X) and water (2X) – excess liquid should be shaken from the tool after each rinse and dried with paper and kimwipes. Thereafter, 50 µl of Membrane Protein will be added to each well (a control well comprising membranes without the GPCR Fusion Protein was also utilized), and pre-incubated for 5-10 minutes at room temperature. Thereafter, 50µl of [^{35}S]GTPγS (0.6 nM) in Binding Buffer will be added to each well, followed by incubation on a shaker for 60 minutes at room temperature (again, in this example, plates were covered with foil). The assay will then be stopped by spinning of the plates at 4000 RPM for 15 minutes at 22°C. The plates will then be aspirated with an 8 channel manifold and sealed with plate covers. The plates will then be read on a Wallac 1450 using setting "Prot. #37" (as per manufacturer instructions).

B. Cyclic AMP Assay

Another assay approach to directly identified candidate compound was accomplished by utilizing a cyclase-based assay. In addition to direct identification, this assay approach can be utilized as an independent approach to provide confirmation of the results from the [^{35}S]GTPγS approach as set forth above.

A modified Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) was preferably utilized for direct identification of candidate compounds as inverse agonists and agonists to constitutively activated orphan GPCRs in accordance with the following protocol.

Transfected cells were harvested approximately three days after transfection. Membranes were prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCl_2$. Homogenization was performed on ice using a Brinkman Polytron™ for approximately 10 seconds. The resulting homogenate is centrifuged at 49,000 X g for 15 minutes at 4°C. The resulting pellet was then resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized for 10 seconds, followed by centrifugation at

49,000 x g for 15 minutes at 4°C. The resulting pellet was then stored at -80°C until utilized. On the day of direct identification screening, the membrane pellet was slowly thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCl_2$, to yield a final protein concentration of 0.60mg/ml (the resuspended membranes are placed on ice until use).

cAMP standards and Detection Buffer [comprising 2 μCi of tracer ^{125}I-cAMP (100 μl) to 11 ml Detection Buffer] were prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer was prepared fresh for screening and contained 20mM HEPES, pH 7.4, 10mM $MgCl_2$, 20mM phospocreatine (Sigma), 0.1 units/ml creatine phosphokinase (Sigma), 50 μM GTP (Sigma), and 0.2 mM ATP (Sigma); Assay Buffer was then stored on ice until utilized.

Candidate compounds identified as per above (if frozen, thawed at room temperature) were added, preferably, to 96-well plate wells (3μl/well; 12μM final assay concentration), together with 40 μl Membrane Protein (30μg/well) and 50μl of Assay Buffer. This admixture was then incubated for 30 minutes at room temperature, with gentle shaking.

Following the incubation, 100μl of Detection Buffer was added to each well, followed by incubation for 2-24 hours. Plates were then counted in a Wallac MicroBeta™ plate reader using "Prot. #31" (as per manufacturer instructions).

Example 9

MELANOPHORE TECHNOLOGY

Melanophores are skin cells found in lower vertebrates. They contain pigmented organelles termed melanosomes. Melanophores are able to redistribute these melanosomes along a microtubule network upon G-protein coupled receptor (GPCR) activation. The result of this pigment movement is an apparent lightening or darkening of the cells. In melanophores, the decreased levels of intracellular cAMP that result from activation of a Gi-coupled receptor cause melanosomes to migrate to the center of the cell, resulting in a dramatic lightening in color. If cAMP levels are then raised, following activation of a Gs-coupled receptor, the melanosomes are re-dispersed and the cells appear dark again. The increased levels of diacylglycerol that result from activation of Gq-coupled receptors can also induce this re-dispersion. In addition, the technology is also suited to the study of certain receptor tyrosine kinases. The response of the melanophores takes place within minutes of receptor activation and results in a simple, robust color change. The response can be easily detected using a conventional absorbance microplate reader or a modest video imaging system. Unlike other skin cells, the melanophores derive from the neural crest and appear to express a full complement of signaling proteins. In particular, the cells express an extremely wide range of G-proteins and so are able to functionally express almost all GPCRs.

Melanophores can be utilized to identify compounds, including natural ligands, against GPCRs. This method can be conducted by introducing test cells of a pigment cell line capable of dispersing or aggregating their pigment in response to a specific stimulus and expressing an exogenous clone coding for the GCPR. A stimulant, *e.g.*, melatonin, sets an initial state of pigment disposition wherein the pigment is aggregated within the test cells if activation of the GPCR induces pigment dispersion. However, stimulating the cell with a stimulant to set an initial state of pigment disposition wherein the pigment is dispersed if activation of the GPCR induces pigment aggregation. The test cells are then contacted with chemical compounds, and it is determined whether the pigment disposition in the cells changed from the initial state of pigment disposition. Dispersion of pigments cells due to the candidate compound, including but not limited to a ligand, coupling to the GPCR will appear dark on a petri dish, while aggregation of pigments cells will appear light.

Materials and methods will be followed according to the disclosure of U.S. Patent Number 5,462,856 and U.S. Patent Number 6,051,386. These patent disclosures are hereby incorporated by reference in their entirety.

Melanophores were transfected by electroporation with plasmids coding for the GPCRs, for example **hRUP25**. Pre-screening of the GPCRs in melanophores was performed in the absence of nicotinic acid following the protocol below to determine the G protein coupling. This pre-screen evidenced that **hRUP25** (Figure 2) is strongly Gi-coupled.

The cells were plated in 96-well plates (one receptor per plate). 48 hours post-transfection, half of the cells on each plate were treated with 10nM melatonin. Melatonin activates an endogenous Gi-coupled receptor in the melanophores and causes them to aggregate their pigment. The remaining half of the cells were transferred to serum-free medium 0.7X L-15 (Gibco). After one hour, the cells in serum-free media remained in a pigment-dispersed state while the melatonin-treated cells were in a pigment-aggregated state. At this point, the cells were treated with a dose response of nicotinic acid (Sigma). If the plated GPCRs bound to nicotinic acid, the melanophores would be expected to undergo a color change in response to the compound. If the receptor were either a Gs or Gq coupled receptor, then the melatonin-aggregated melanophores would undergo pigment dispersion. In contrast, if the receptor was a Gi-coupled receptor, then the pigment-dispersed cells would be expected to undergo a dose-dependent pigment aggregation.

Melanophores transfected with **hRUP25** were treated with nicotinic acid. Upon this treatment, the cells underwent pigment aggregation in a dose-dependent manner. **hRUP25**-expressing cells that were pre-aggregated with melatonin did not disperse upon nicotinic acid treatment, which is consistent with the receptor being a Gi-coupled receptor. *See*, Figure 3 and *infra*.

To confirm and extend these results, melanophores were transfected with a range of **hRUP25** DNA from 0 to 10μg. As controls, melanophores were also transfected with 10μg of α_{2A} Adrenergic receptor (a known Gi-coupled receptor) and salmon sperm DNA (Gibco), as a mock transfection. On day 3, the cells were again incubated for 1 hour in serum-free L-15 medium (Gibco) and remained in a pigment-dispersed state. The cells were then treated with a dose response of nicotinic acid. *See*, Figure 3A. Figure 3A depicts the aggregation response of nicotinic acid at melanophores transfected with various ranges of **hRUP25**. At 10μg of **hRUP25**, the EC_{50} for nicotinic acid is about 54nM. Stated differently, at very low concentrations, nicotinic acid evidences binding to **hRUP25**.

Reference is now made to Figure 3B. In Figure 3B, both the mock transfected and α_{2A} transfected cells did not respond to nicotinic acid. This data evidences that nicotinic acid binds specifically to the Gi-coupled receptor **hRUP25**.

The data show that the greater the amount of **hRUP25** plasmid DNA transfected, the greater the magnitude of the observed aggregation response. Collectively these data indicate that **hRUP25**: 1) is a Gi-coupled receptor that 2) binds to nicotinic acid.

As set forth herein, nicotinic acid is a ligand for, and agonist of, human, mouse and rat **RUP25**. It is further shown that human, mouse and rat **RUP25** are Gi-coupled. Additionally, human, mouse, and rat **RUP25** may be used in methods described herein to identify antagonists, agonists, inverse agonists, partial agonists, allosteric enhancers, and negative allosteric modulators. As discussed *supra*, methods of modifying nicotinic acid receptor activity in adipocytes using a modulator of the receptor are set forth. Preferably, the modulator is an agonist.

Example 10

NICOTINIC ACID INDUCED-INOSITOL PHOSPHATES ACCUMULATION IN 293 CELLS CO-EXPRESSING hRUP AND GqΔGi

Figure 4 illustrates the nicotinic acid induced-inositol phosphates (IPs) accumulation in HEK293 cells co-expressing **hRUP25** and the chimeric Gαq-subunit in which the last five amino acids have been replaced with the corresponding amino acids of Gαi (GqΔGi). This construct has been shown to convert the signaling of a Gi-coupled receptor to the Gq pathway (i.e. accumulation of inositol phosphates) in response to receptor activation. Cells transfected with GqΔGi plus either empty plasmid or the constitutively activated α_{2A}AR (α_{2A}K) served as controls for the IP assay which are non-responsive to nicotinic acid.

Example 11

NICOTINIC ACID AND NICOTINE INDUCED-INHIBITION OF FORSKOLIN STIMULATED cAMP ACCUMULATION IN hRUP25-CHO CELL STABLE LINE #46

Figure 5A is a set of immunofluorescent photomicrographs illustrating the expression of hemaglutinin(HA)-tagged **hRUP25** in a stably transfected line of CHO cells (top; clone #46). No significant labeling is detected in mock stably-transfected CHO cells (Mock). The lower panels identify the nuclear (DAPI) staining of cells in the same field.

Figure 5B illustrates nicotinic acid and nicotine induced-inhibition of forskolin stimulated cAMP accumulation in **hRUP25**-CHO cell stable line #46 (described in preceding paragraph). The EC_{50} for nicotinic acid is 23.6nM and that for nicotine is 9.8μM.

Example 12

hRUP25 AND mRUP25 INHIBIT TSHR INDUCED-cAMP ACCUMULATION FOLLOWING ACTIVATION BY NICOTINIC ACID

Figure 6 indicates that, in response to nicotinic acid, both **hRUP25** and the mouse ortholog **mRUP25** can inhibit TSHR stimulated cAMP production (in the presence and absence of TSH).

Example 13

hRUP25 AND mRUP25 BIND TO NICOTINIC ACID SPECIFICALLY AND WITH HIGH AFFINITY

Figure 7 shows the saturation binding curves of [^{3}H]nicotinic acid ([^{3}H]NA) to membranes prepared from HEK293 cells transiently expressing either **hRUP25** or **mRUP25**. Note the significant binding of [^{3}H]NA relative to either that found in membranes derived from mock transfected cells or in the presence of an excess of non-labeled nicotinic acid (200μM).

Radioligand binding was done as follows. Media was removed from cells grown in culture [either stably or transiently transfected with negative control (empty plasmid) or with the individual receptors **hRUP25**, **mRUP25**, **rRUP25** and cells were scraped and homogenized in buffer containing 15mM HEPES, 5mM EDTA, 5mM EGTA, plus protease inhibitors (leupeptin, PMSF and pepstatin). Membranes were harvested following centrifugation at 30,000 X g, 4°C for 30min. Membranes were then resuspended and re-homogenized in CHAPS binding buffer (50mM Tris-HCl and 0.02% CHAPS, pH 7.4). Aliquots were taken for protein analysis *via* the Bradford protein assay and normalized such that each binding reaction contained the same amount of membrane protein (25-50μg). 50nM [^{3}H]nicotinic acid was added to each sample and either buffer (for total samples) or a desired amount of non-labeled compound (at the same volumes and in the same diluent) was added and

the reactions were left at room temperature gently shaking for 1hr. Free ligand was separated from bound ligand *via* rapid filtration onto a filter. Appropriate scintilant was added to each sample and counted in an appropriate scintillation counter. Data was analyzed using Excel and PrismGraph. In some cases radioligand binding was performed using a scintillation proximity assay (SPA) in which case the samples did not require filtration or the addition of scintilant.

Example 14

THE RANK ORDER OF POTENCY OF COMPOUNDS ON HRUP25 CLOSELY MATCHES THAT OF THE PHARMACOLOGICALLY DEFINED NICOTINIC ACID RECEPTOR

Figure 8 is a table comparing the rank order of potency of various compounds on **hRUP25** and the pharmacologically defined nicotinic acid receptor. The potencies at **hRUP25** derived both by a functional analysis measuring the inhibition of forskolin induced cAMP production and competitive radioligand binding assays, closely match the order of potencies of the pharmacologically defined nicotinic acid receptor.

Example 15

NICOTINIC ACID AND RELATED COMPOUNDS INHIBIT ISOPROTERENOL INDUCED LIPOLYSIS IN RAT EPIDIMAL FAT DERIVED ADIPOCYTES

Figure 9A depicts nicotinic acid and related compounds inhibiting isoproterenol induced lipolysis in rat epidimal fat derived adipocytes at a concentration of 10μM. P-3-T represents 3-tetrazole-5-pyridine.

Figure 9B illustrates a nicotinic acid dose-dependent inhibition of isoproterenol induced-lipolysis in rat epidimal fat derived adipocytes. Note the rightward shift in the dose-response curves with increasing concentrations of nicotinic acid.

Lipolysis assays were done following the isolation of adipocytes from rat or human. The source of fat from rats was the epididymal fat and from humans was either subcutaneous or omental. Cells were isolated following collagenase digestion and floatation. An elevation of intracellular cAMP levels and concomitant activation of lipolysis *via* hormone sensitive lipase was accomplished using isoproterenol, forskolin, 3-isobutyl-1-methyl-xanthine (IBMX) or a combination thereof at concentrations and times determined empirically and depending on the source of tissue. Lipolysis was allowed to continue for the desired time in the presence or absence of drug (*e.g.* nicotinic acid, P-3-T, etc). Data was analyzed using Excel and PrismGraph.

Example 16

DOSE-DEPENDENT INHIBITION OF ISOPROTERENOL INDUCED-LIPOLYSIS IN HUMAN, SUBCUTANEOUS-DERIVED, PRIMARY ADIPOCYTES VIA NICOTINIC ACID AND P-3-T

Figure 10 illustrates the ability of both nicotinic acid and the related compound P-3-T (3-tetrazole-5-pyridine) to inhibit isoproterenol induced lipolysis in adipocyte primary cultures

derived from human subcutaneous fat in a dose-dependant manner. The EC_{50} value for nicotinic acid and P-3-T were 716nM and 218nM respectively.

Example 17

SUMMARY: HRUP25, MRUP25 AND RRUP25.

TABLE D

Disclosed Nicotinic Acid Receptor Sub-Family GPCRs	Expression by Adipocytes or Adipose	Gi-Coupled (Lowers the Level of Intracellular cAMP)	Shown to Inhibit Intracellular Lipolysis	Agonist
hRUP25	yes	yes	yes	nicotinic acid; nicotine; *see* Figure 8
mRUP25	yes	yes	yes	nicotinic acid
rRUP25	yes	yes	yes	nicotinic acid

Example 18

RODENT DIABETES MODELS

Rodent models of type 2 diabetes associated with obesity and insulin resistance have been developed. Genetic models such as db/db and ob/ob [*see* Diabetes (1982) 31:1-6] in mice and fa/fa in zucker rats have been developed for understanding the pathophysiology of disease and for testing candidate therapeutic compounds [Diabetes (1983) 32:830-838; Annu Rep Sankyo Res Lab (1994) 46:1-57]. The homozygous animals, C57 BL/KsJ-db/db mice developed by Jackson Laboratory are obese, hyperglycemic, hyperinsulinemic and insulin resistant [J Clin Invest (1990) 85:962-967], whereas heterozygotes are lean and normoglycemic. In the db/db model, mice progressively develop insulinopenia with age, a feature commonly observed in late stages of human type 2 diabetes when sugar levels are insufficiently controlled. Since this model resembles that of human type 2 diabetes, the compounds of the present invention are tested for activities including, but not limited to, lowering of plasma glucose and triglycerides. Zucker (fa/fa) rats are severely obese, hyperinsulinemic, and insulin resistant {Coleman, Diabetes (1982) 31:1; E Shafrir in Diabetes Mellitus, H Rifkin and D Porte, Jr, Eds [Elsevier Science Publishing Co, New York, ed. 4, (1990), pp. 299-340]}, and the fa/fa mutation may be the rat equivalent of the murine db mutation [Friedman et al, Cell (1992) 69:217-220; Truett et al, Proc Natl Acad Sci USA (1991) 88:7806]. Tubby (tub/tub) mice are characterized by obesity, moderate insulin resistance and hyperinsulinemia without significant hyperglycemia [Coleman et al, Heredity (1990) 81:424].

The present invention encompasses the use of compounds of the invention for reducing the insulin resistance and hyperglycemia in any or all of the above rodent diabetes models, in humans with type 2 diabetes or other preferred metabolic-related disorders or disorders of lipid metabolism described previously, or in models based on other mammals. Plasma glucose and insulin levels will be tested, as well as other factors including, but not limited to, plasma free fatty acids and triglycerides.

In Vivo Assay for Anti-Hyperglycemic Activity of Compounds of the Invention

Genetically altered obese diabetic mice (db/db) (male, 7-9 weeks old) are housed (7-9 mice/cage) under standard laboratory conditions at 22°C and 50% relative humidity, and maintained on a diet of Purina rodent chow and water *ad libitum*. Prior to treatment, blood is collected from the tail vein of each animal and blood glucose concentrations are determined using One Touch Basic Glucose Monitor System (Lifescan). Mice that have plasma glucose levels between 250 to 500 mg/dl are used. Each treatment group consists of seven mice that are distributed so that the mean glucose levels are equivalent in each group at the start of the study. db/db mice are dosed by micro-osmotic pumps, inserted using isoflurane anesthesia, to provide compounds of the invention, saline, or an irrelevant compound to the mice subcutaneously (s.c.). Blood is sampled from the tail vein at intervals thereafter and analyzed for blood glucose concentrations. Significant differences between groups (comparing compounds of the invention to saline-treated) are evaluated using Student t-test.

Example 19

MOUSE ATHEROSCLEROSIS MODEL

Adiponectin-deficient mice generated through knocking out the adiponectin gene have been shown to be predisposed to atherosclerosis and to be insulin resistant. The mice are also a suitable model for ischemic heart disease [Matsuda, M et al. J Biol Chem (2002) July, and references cited therein, the disclosures of which are incorporated herein by reference in their entirety].

Adiponectin knockout mice are housed (7-9 mice/cage) under standard laboratory conditions at 22°C and 50% relative humidity. The mice are dosed by micro-osmotic pumps, inserted using isoflurane anesthesia, to provide compounds of the invention, saline, or an irrelevant compound to the mice subcutaneously (s.c.). Neointimal thickening and ischemic heart disease are determined for different groups of mice sacrificed at different time intervals. Significant differences between groups (comparing compounds of the invention to saline-treated) are evaluated using Student t-test.

Example 20

***In Vitro* Biological Activity**

A modified Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) was utilized for direct identification of candidate compounds as agonists to hRUP25 in accordance with the following protocol:

Stably transfected CHO cells (clone 46) were harvested from flasks *via* non-enzymatic means. The cells were washed in PBS and resuspended in the manufacturer's Assay Buffer. Live cells were counted using a hemacytometer and Trypan blue exclusion, and the cell concentration was adjusted to $2x10^6$ cells/ml. cAMP standards and Detection Buffer (comprising 2 μCi of tracer [^{125}I]-cAMP (100 μl) to 11 ml Detection Buffer) were prepared and maintained in accordance with the manufacturer's instructions. Candidate compounds identified as per above (if frozen, thawed at room temperature) were added to their respective wells (preferably wells of a 96-well plate) at increasing concentrations (3μl/well; 12μM final assay concentration). To these wells, 100,000 cells in 50μl of Assay Buffer were added and the mixture was then incubated for 30 minutes at room temperature, with gentle shaking. Following the incubation, 100μl of Detection Buffer was added to each well, followed by incubation for 2-24 hours. Plates were counted in a Wallac MicroBeta™ plate reader using "Prot. #31" (as per manufacturer instructions).

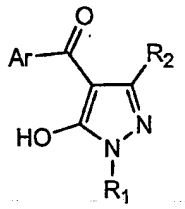
Throughout this application, various publications, patents and published patent applications are cited. The disclosures of these publications, patents and published patent applications referenced in this application are hereby incorporated by reference in their entirety into the present disclosure. Modifications and extension of the disclosed inventions that are within the purview of the skilled artisan are encompassed within the above disclosure and the claims that follow.

Although a variety of expression vectors are available to those in the art, for purposes of utilization for both the endogenous and non-endogenous human GPCRs, it is most preferred that the vector utilized be pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be viable. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



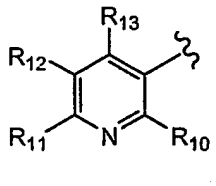
(I)

wherein:

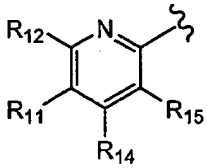
R_1 is alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, or benzyl, where the alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl or benzyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl groups;

R_2 is H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, benzyl, phenyl or heteroaryl, where the alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, benzyl, phenyl or heteroaryl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl groups;

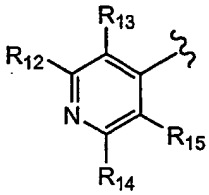
Ar is a pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl of the following formula:



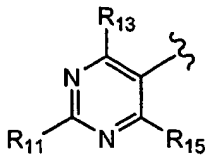
(IIa)

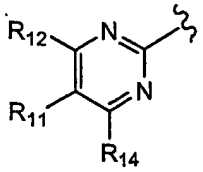


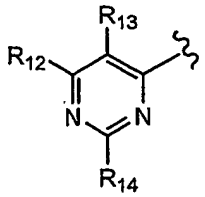
(IIb)

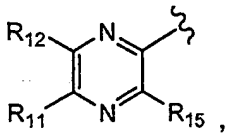


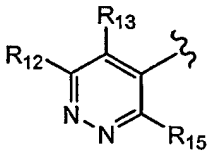
(IIc)

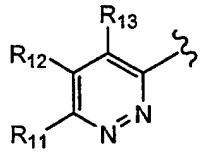

(IIIa)


(IIIb)


(IIIc)


(IVa)


(Va)


(Vb) ;

wherein R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl groups; where alkyl, cycloalkyl, alkenyl, alkynyl, is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl groups; or

one or more N-oxide thereof; or

a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 provided that when Ar is of the Formula **(IIa)** then R_{11} is not a C_1-C_3 haloalkyl.

3. The compound according to claim 1 provided that when Ar is of the Formula **(IIa)** then:

R_{10} is not methyl or phenoxy; or

R_{10} is not an alkyl or haloalkyl substituted with aminoalkyl, aminodialkyl, alkoxy, hydroxyl, haloalkoxy, carboalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl.

4. The compound according to claim 1 provided that when Ar is of the Formula (**IIa**) then R_{12} is not halogen, haloalkyl, alkyl, alkoxy, or alkyl substituted with alkoxy.

5. The compound according to claim 1 provided that when Ar is of the Formula (**IIb**) and:

i) R_1 and R_2 are CH_3, then R_{11} is not a chlorine atom;

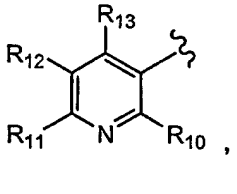
ii) R_1 and R_2 are CH_3, then R_{11} is not a bromine atom;

iii) R_1 and R_2 are CH_3, then R_{11} and R_{12} are both not chlorine atoms or both not bromine atoms;

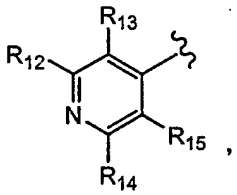
vi) R_1 and R_2 are CH_3, then R_{10}, R_{11} R_{12}, and R_{14} are not all hydrogen atoms; and

v) R_1 is CH_3, and R_2 is CF_3, then R_{11} and R_{12} are both not chlorine atoms..

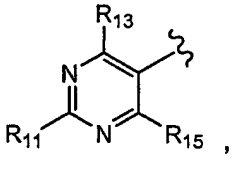
6. The compound according to any one of the claims 2 to 4 wherein Ar is one of the following formulae:



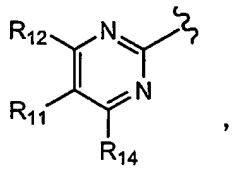
(IIa)



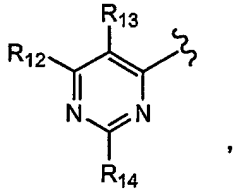
(IIc)



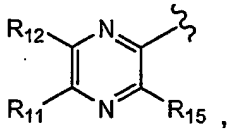
(IIIa)



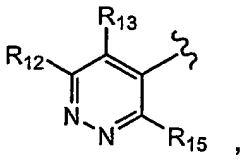
(IIIb)



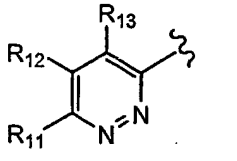
(IIIc)



(IVa)



(Va)



(Vb) ;

R_{10} is a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, haloalkoxy, carboxyl,

carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl group; and

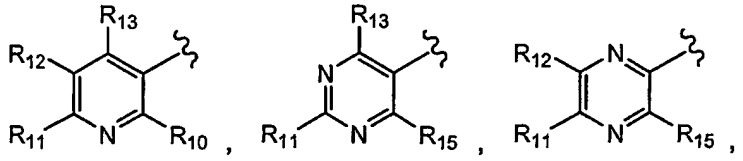
R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl group.

7. The compound according to claim 6 wherein R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, or alkylureyl group.

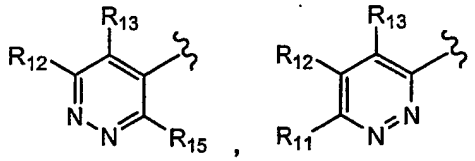
8. The compound according to claim 7 wherein R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, or alkylureyl group.

9. The compound according to claim 8 wherein R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently a H, halogen, hydroxy, cyano, nitro, C_1-C_3 haloalkyl, amino, aminoalkyl, aminodialkyl, C_1-C_3 alkyl.

10. The compound according to claim 9 wherein Ar is one of the following formulae:



(IIa) (IIIa) (IVa)



(Va) (Vb)

11. The compound according to claim 2 wherein:

R_1 is alkyl, or haloalkyl, where the alkyl or haloalkyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkoxy, haloalkoxy, alkylcarboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl or alkylureyl groups.

12. The compound according to claim 11 wherein:

R_2 is H, alkyl, haloalkyl, cycloalkyl, benzyl, phenyl or heteroaryl, where the alkyl, haloalkyl, cycloalkyl, benzyl, phenyl or heteroaryl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl or alkylureyl groups.

13. The compound according to claim 12 wherein:

R_1 is H or alkyl, where the alkyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, amino, aminoalkyl, aminodialkyl; and

R_2 is H, alkyl or phenyl, where the alkyl or phenyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy or haloalkoxy groups.

14. The compound according to claim 13 wherein Ar is Formula (**IIa**); R_{11} is H, halogen, hydroxy, C_1-C_3 alkyl, or amino; and R_{10}, R_{12} and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

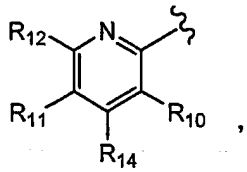
15. The compound according to claim 13 wherein Ar is Formula (**IIIa**); and R_{10}, R_{11}, R_{12}, and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

16. The compound according to claim 13 wherein Ar is Formula (**IVa**); and R_{10}, R_{11}, R_{12}, and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

17. The compound according to claim 13 wherein Ar is Formula (**Va**); and R_{10}, R_{11}, R_{12}, and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

18. The compound according to claim 13 wherein Ar is Formula (**Vb**); and R_{10}, R_{11}, R_{12}, and R_{13} are independently H, halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or amino.

19. The compound according to claim 5 wherein Ar is the following formula:



(IIb)

wherein:

R_{10}, R_{11}, R_{12} and R_{14} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, cycloalkyl, alkoxy, phenoxy, alkenyl, alkynyl, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, arylcarboxamido, heteroarylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, alkylureyl or arylureyl group.

20. The compound according to claim 19 wherein R_{10}, R_{11}, R_{12} and R_{14} are independently a H, halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, or alkylureyl group.

21. The compound according to claim 20 wherein R_{10}, R_{11}, R_{12} and R_{14} are independently a H, halogen, hydroxy, cyano, nitro, C_1-C_3 haloalkyl, amino, aminoalkyl, aminodialkyl, C_1-C_3 alkyl group.

22. The compound according to claim 21 wherein:

R_2 is H, alkyl, haloalkyl, cycloalkyl, benzyl, phenyl or heteroaryl, where the alkyl, haloalkyl, cycloalkyl, benzyl, phenyl or heteroaryl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy, haloalkoxy, carboxyl, carboalkoxy, alkylcarboxamido, heterocyclic carboxamido, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl or alkylureyl groups.

24. The compound according to claim 23 wherein:

R_1 is H or alkyl, where the alkyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, amino, aminoalkyl, aminodialkyl; and

R_2 is H, alkyl or phenyl, where the alkyl or phenyl is optionally substituted with one or more halogen, hydroxy, cyano, nitro, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy or haloalkoxy groups.

25. The compound according to claim 24 wherein:

R_1 is alkyl optionally substituted with one or more halogen, hydroxy, amino, aminoalkyl, aminodialkyl.

26. The compound according to claim 24 wherein:

R_2 is H or alkyl, where the alkyl is optionally substituted with one or more halogen, hydroxy, haloalkyl, amino, aminoalkyl, aminodialkyl, alkyl, alkoxy or haloalkoxy groups.

27. A compound of the formula:

(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-methyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-ethyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-isopropyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-butyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-isobutyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-neopentyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-cyclopropyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-cyclopentyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-cyclohexyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-benzyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-phenyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-(3-pyridyl)-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-methyl-3-(2-pyridyl)-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-3-methyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-3-ethyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-3-propyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-3-isopropyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;

(5-hydroxy-1-ethyl-3-butyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-3-isobutyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-3-neopentyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-3-cyclopropyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-3-cyclopentyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-3-cyclohexyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-3-benzyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-3-phenyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-3-(3-pyridyl)-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-ethyl-3-(2-pyridyl)-1H-pyrazol-4-yl)-pyridin-3-yl-methanone;
(5-hydroxy-1-(2,2,2-trifluoroethyl)-3-propyl-1H-pyrazol-4-yl)-pyridin-3-yl-methanone; and
(5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(5-fluoro-pyridin-3-yl)-methanone.

28. A compound of the formula:

(5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyridin-2-yl)-methanone;
(5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyrimidin-5-yl)-methanone;
(5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyrazin-3-yl)-methanone;
(5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyridazin-4-yl)-methanone; and
(5-hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)-(pyridazin-3-yl)-methanone.

29. A pharmaceutical composition comprising a compound of any one of the claims 1-28.

30. A method of prophylaxis or treatment of a metabolic disorder comprising the administrating to a patient in need of such administration a therapeutically or prophylactically effective amount of a compound according to any one of the claims 1-28.

31. The method according to claim 30 wherein the metabolic disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes.

32. The method according to claim 31 wherein the metabolic disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes.

33. Use of a compound according to any one of the claims 1-28 for production of a medicament for use in prophylaxis or treatment of a metabolic disorder.

34. The use of the compound according to claim 33 wherein the metabolic disorder is dyslipidemia; atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease and type 2 diabetes.

35. The use of the compound according to claim 34 wherein the metabolic disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes.

36. A method of prophylaxis or treatment of a metabolic disorder comprising the administrating to a patient in need of such administration a therapeutically or prophylactically effective amount of a compound according to any one of the claims 1 to 28 in combination with one or more agent selected from the group consisting of α-glucosidase inhibitor, aldose reductase inhibitor, biguanide, HMG-CoA reductase inhibitor, squalene synthesis inhibitor, fibrate, LDL catabolism enhancer, angiotensin converting enzyme inhibitor, insulin secretion enhancer and thiazolidinedione.

37. The method according to claim 36 wherein the agent is a α-glucosidase inhibitor.

38. The method according to claim 37 wherein the α-glucosidase inhibitor is acarbose, voglibose or miglitol.

39. The method according to claim 38 wherein the α-glucosidase inhibitor is voglibose.

40. The method according to claim 36 wherein the agent is an aldose reductase inhibitor.

41. The method according to claim 40 wherein the aldose reductase inhibitor is tolurestat; epalrestat; imirestat; zenarestat; zopolrestat; or sorbinil.

42. The method according to claim 36 wherein the agent is a biguanide.

43. The method according to claim 42 wherein the biguanide is phenformin, metformin, or buformin.

44. The method according to claim 43 wherein the biguanide is metformin.

45. The method according to claim 36 wherein the agent is a HMG-CoA reductase inhibitor.

46. The method according to claim 45 wherein the HMG-CoA reductase inhibitor is rosuvastatin, pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin.

47. The method according to claim 36 wherein the agent is a fibrate.

48. The method according to claim 47 wherein the fibrate is bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, or theofibrate.

49. The method according to claim 36 wherein the agent is an angiotensin converting enzyme inhibitor.

50. The method according to claim 49 wherein the angiotensin converting enzyme inhibitor is captopril, enalapril, alacepril, delapril; ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril or trandolapril.

51. The method according to claim 36 wherein the agent is an insulin secretion enhancer.

52. The method according to claim 51 wherein the insulin secretion enhancer is tolbutamide; chlorpropamide; tolazamide; acetohexamide; glycopyramide; glibenclamide; gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolcyclamide, glimepiride, nateglinide, or mitiglinide.

53. The method according to claim 36 wherein the agent is a thiazolidinedione.

54. The method according to claim 53 wherein the thiazolidinedione is rosiglitazone or pioglitazone.

55. The method according to claim 54 wherein the thiazolidinedione is rosiglitazone.

5

Figure 1

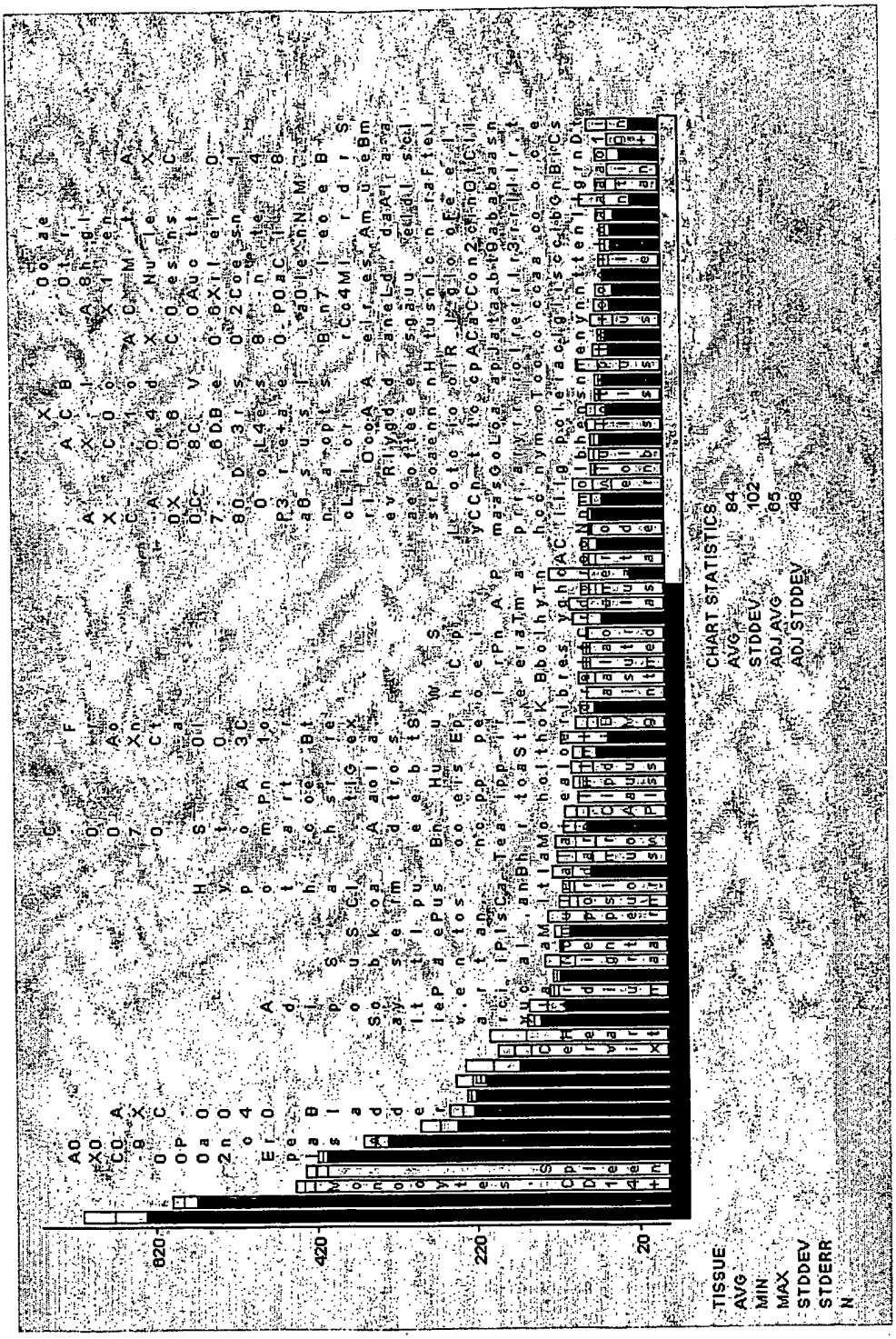
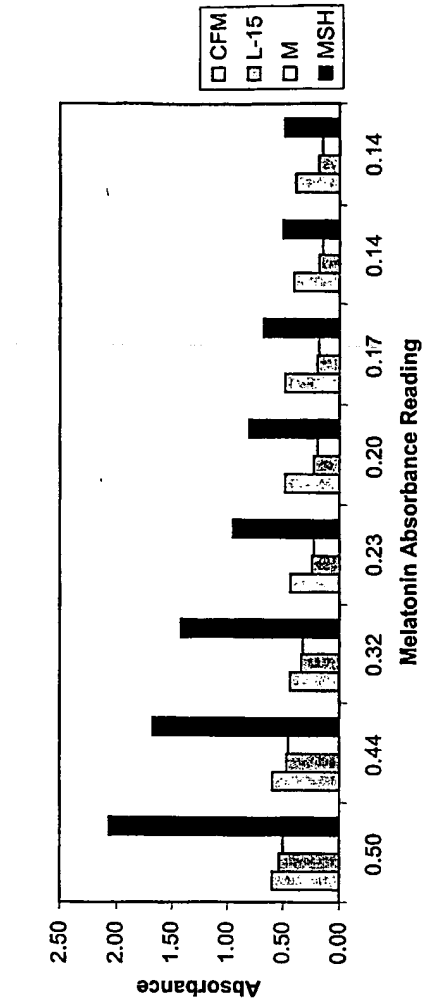

620
420
220
20
CHART STATISTICS
AVG 84
STDDEV 102
ADJ AVG 65
ADJ STDDEV 48
TISSUE
AVG
MIN
MAX
STDDEV
STDERR
N

Figure 2

RUP25 G_i - coupled constitutive activity in melanophore



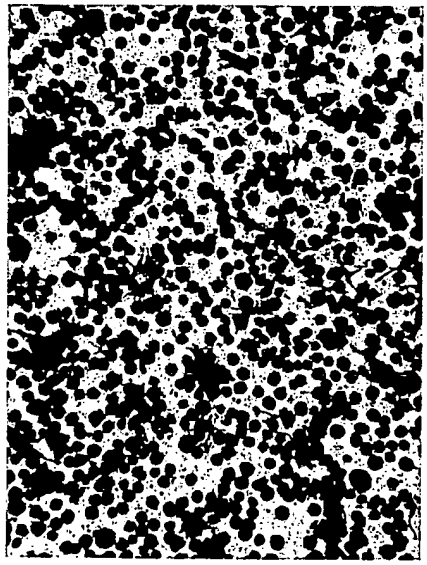


Figure 3A

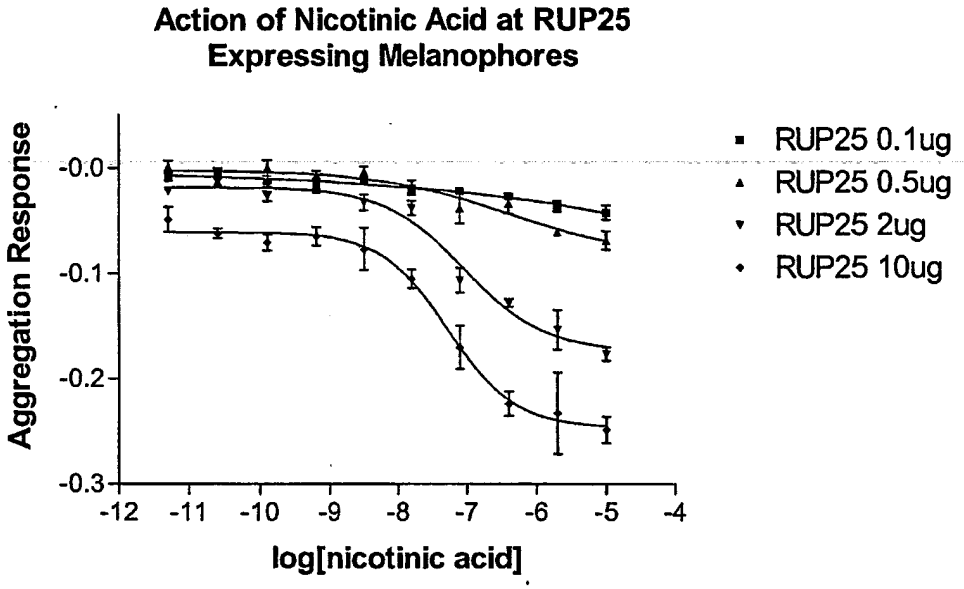


Figure 3B

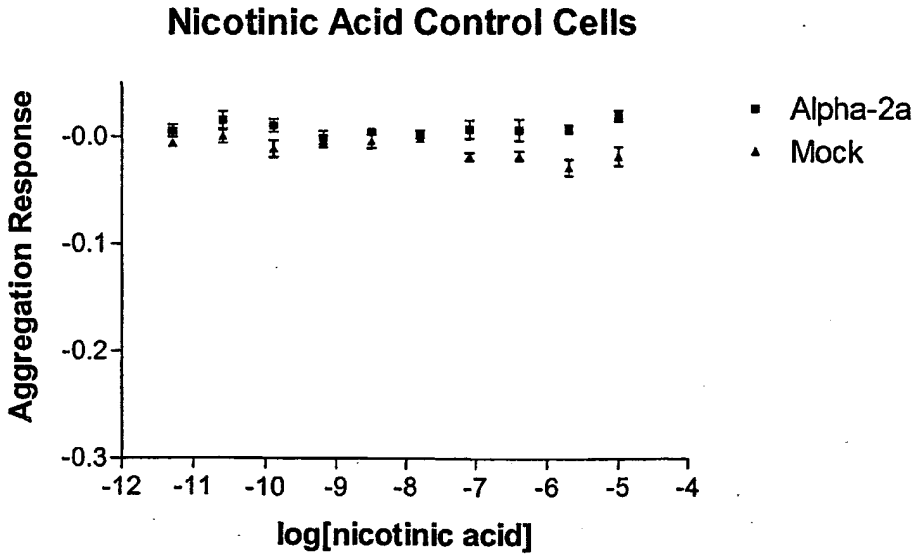


Figure 4
Nicotinic acid induced-IPs accumulation in 293 cells co-expressing hRUP25 and GqΔGi

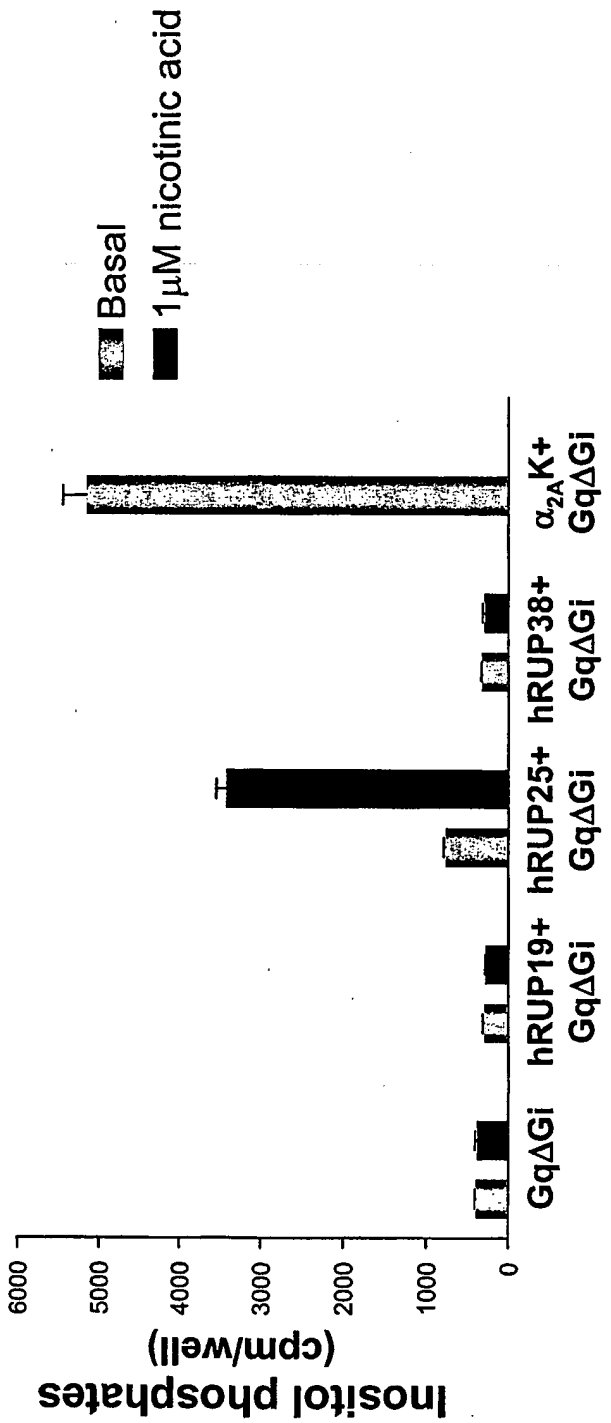


Figure 5A
hRUP25-CHO stable clone identified by anti-HA immunofluorescence staining

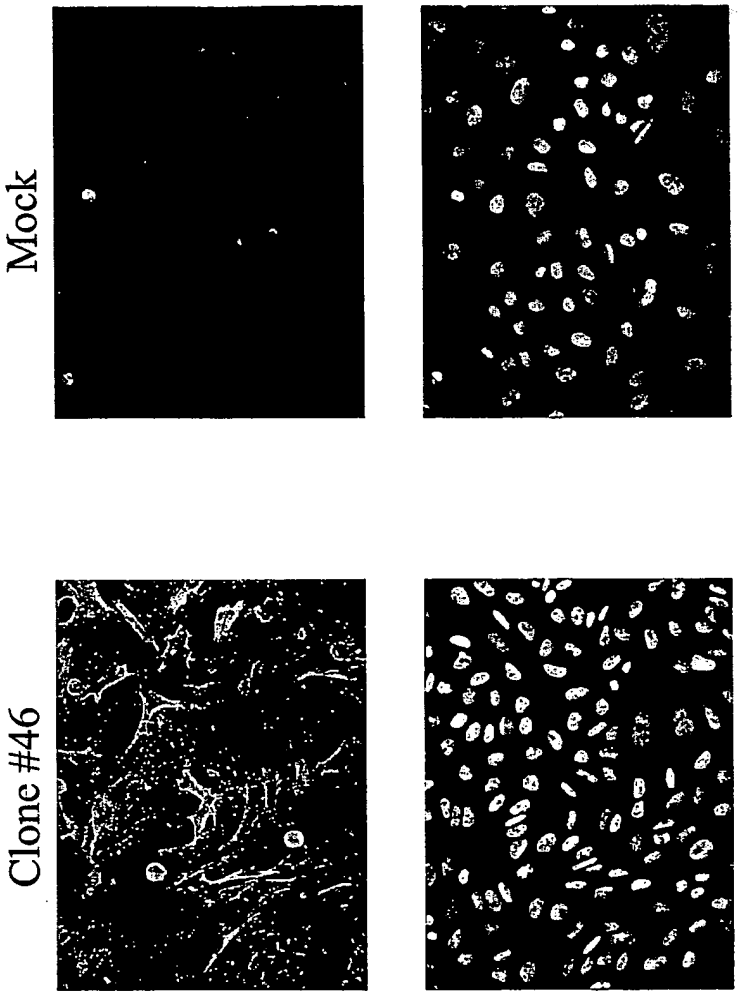


Figure 5B
Nicotinic acid and nicotine induced-inhibition of forskolin stimulated cAMP accumulation in hRUP25-CHO cell stable line #46

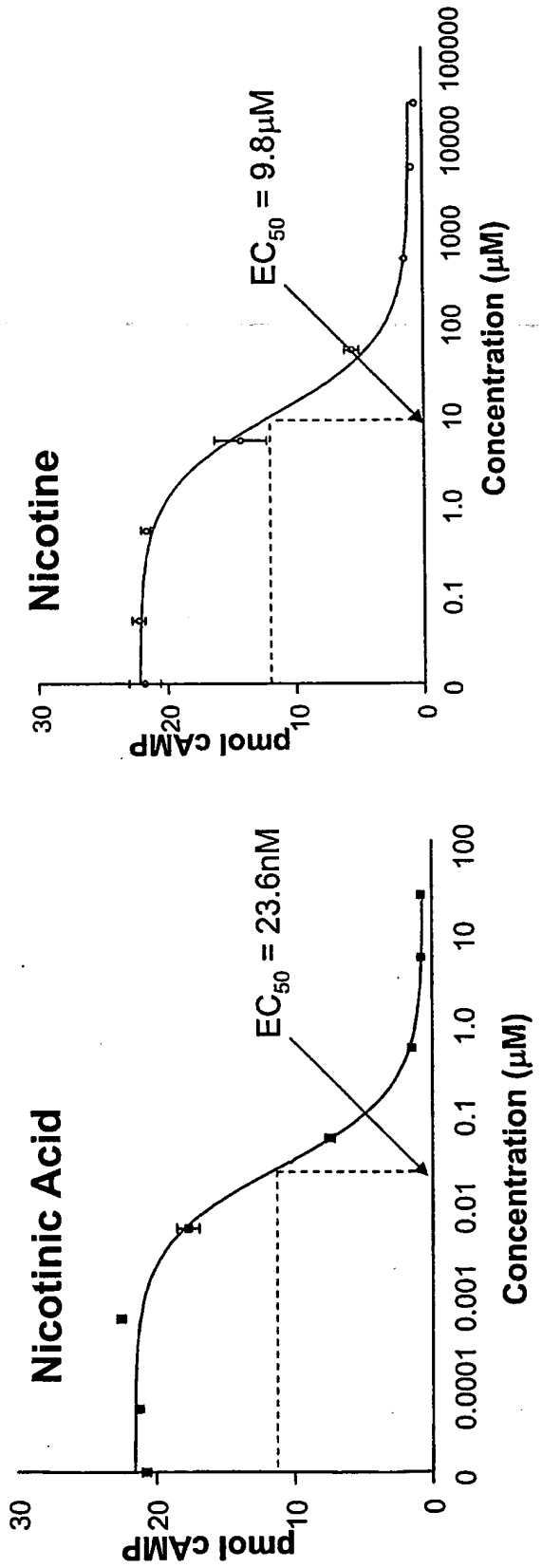


Figure 6
hRUP25 and mRUP25 inhibit TSHR induced-cAMP accumulation following activation by nicotinic acid

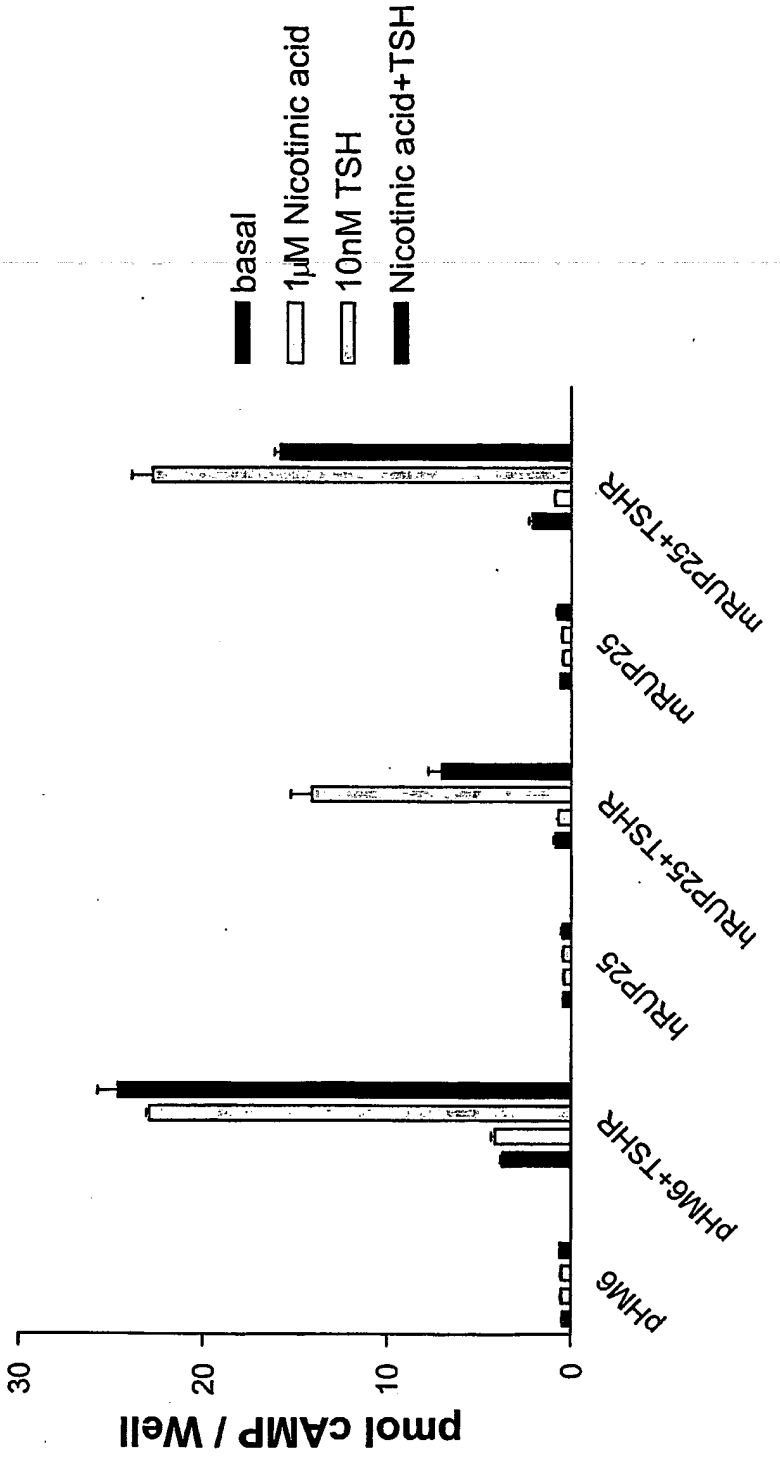


Figure 7
hRUP25 and mRUP25 bind to nicotinic acid specifically and with high affinity

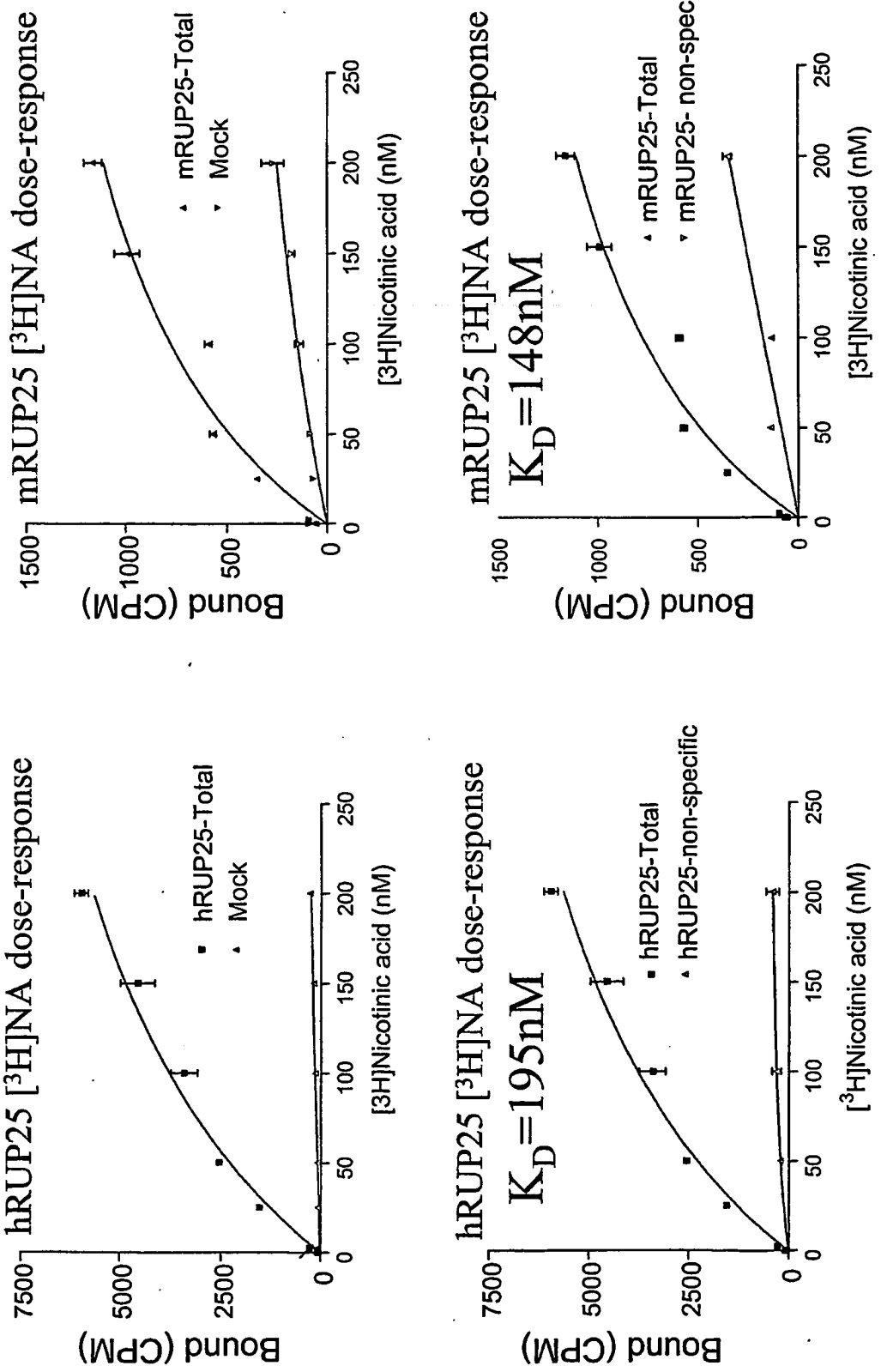


Figure 8

The rank order of potency of compounds on hRUP25 closely matches that of the pharmacologically defined nicotinic acid receptor

	EC 50 (μM)			
Compound	**Adipocytes***	**Spleen***	**hRUP25†**	**hRUP25 (K_d)‡**
Nicotinic acid	1.42	0.703	0.04	0.14
Pyridazine-4-carboxylic acid	3.76	3.14	N.D.	2.19
Acipimox	10.3	6.56	2	2.68
3-Pyridine-acetic acid	16.4	21.8	3	1.64
Pyrazine-2-carboxylic acid	26	22	4	4.14
5-Methylnicotinic acid	30.2	30.0	7	3.58
5-Methylpyrazine-2-carboxylic acid	52.0	14.5	7	7.36
6-Methylnicotinic acid	72.6	53.7	34	21.95
Nicotinic acid-1-oxide	80.4	73.7	120	55.25
2-Hydroxynicotinic acid	132	N.D.	130	145.4
Furane-3-carboxylic acid	142	N.D.	110	130.6
Nicotinamide	>1000	>1000	>1000	128.2

N.D., not determined.

* From Lorenzen,A. *et. al. Mol.Pharmacol.* 59 (2):349-357, 2001.

† Arena data, inhibition of forskolin-induced cAMP production in hRUP25-CHO stable line #46.

‡ Arena data, [^{3}H]nicotinic acid radioligand binding assay on membranes derived from hRUP25-CHO stable line #46.

Figure 9A
Nicotinic acid and related compounds inhibit isoproterenol induced lipolysis in rat epidimal fat derived adipocytes

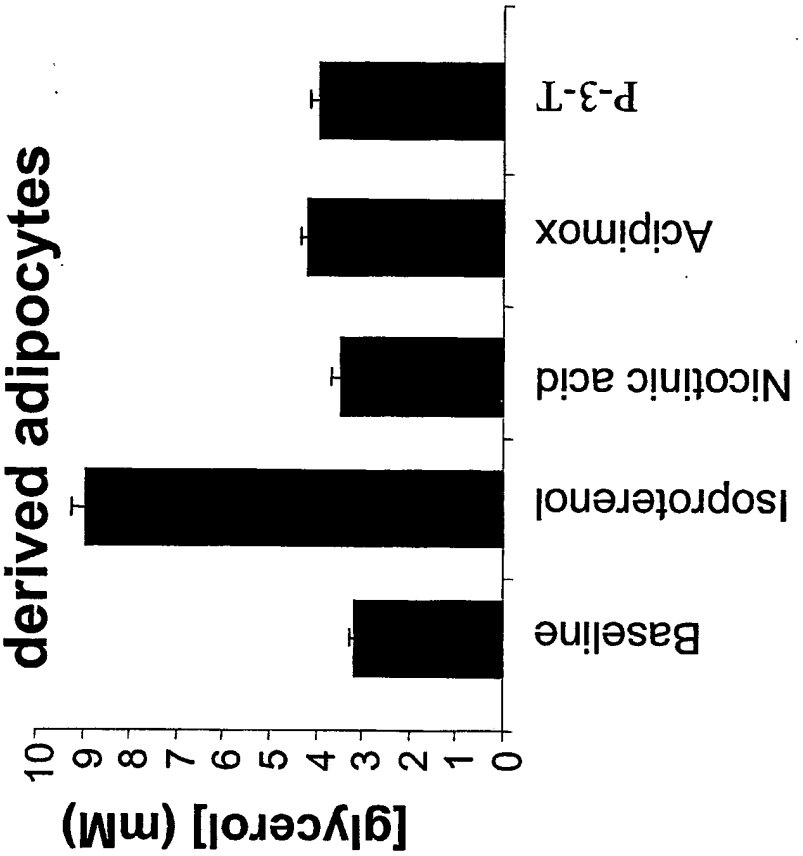


Figure 9B

Nicotinic acid dose-dependent inhibition of isoproterenol induced-lipolysis in rat, epidimal fat derived adipocytes

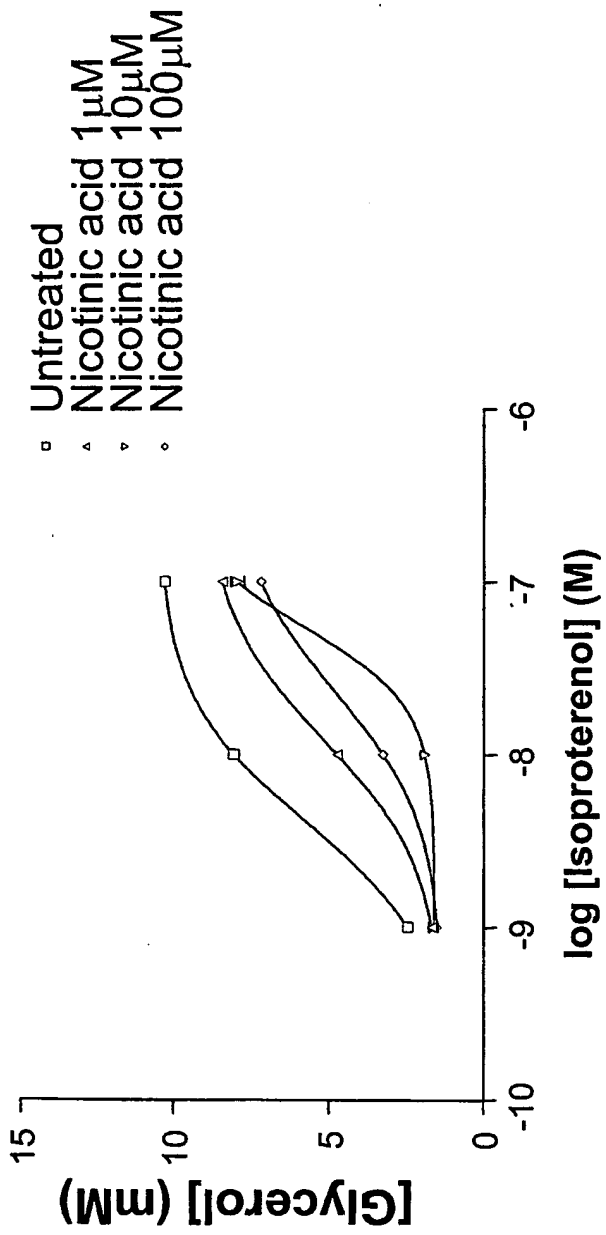
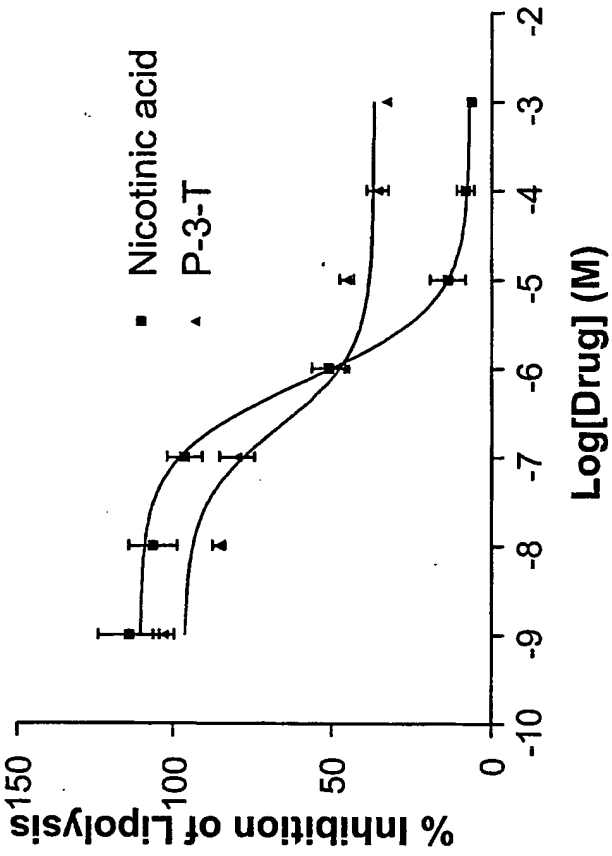


Figure 10
Dose-dependent inhibition of isoproterenol induced-lipolysis in human, subcutaneous-derived, primary adipocytes *via* nicotinic acid and P-3-T



28.WO1.ST25
SEQUENCE LISTING

<110> Arena Pharmaceuticals, Inc.
Semple, Graeme
Shin, Young Jun

<120> HYDROXYPYRAZOLES AND METHODS OF PROPHYLAXIS OR TREATMENT OF METABOLIC-RELATED DISORDERS THEREOF

<130> 28.WO1

<150> 60/416,193
<151> 2002-10-04

<150> 60/417,120
<151> 2002-10-07

<160> 14

<170> PatentIn version 3.2

<210> 1
<211> 1092
<212> DNA
<213> Homo sapien

<400> 1
atgaatcggc accatctgca ggatcacttt ctggaaatag acaagaagaa ctgctgtgtg 60

ttccgagatg acttcattgt caaggtgttg ccgccggtgt tggggctgga gtttatcttc 120

gggcttctgg gcaatggcct tgccctgtgg attttctgtt tccacctcaa gtcctggaaa 180

tccagccgga ttttcctgtt caacctggca gtggctgact ttctactgat catctgcctg 240

cccttcctga tggacaacta tgtgaggcgt tgggactgga agtttgggga catcccttgc 300

cggctgatgc tcttcatgtt ggctatgaac cgccagggca gcatcatctt cctcacggtg 360

gtggcggtag acaggtattt ccgggtggtc catccccacc acgccctgaa caagatctcc 420

aatcggacag cagccatcat ctcttgcctt ctgtggggca tcactattgg cctgacagtc 480

cacctcctga agaagaagat gccgatccag aatggcggtg caaatttgtg cagcagcttc 540

agcatctgcc ataccttcca gtggcacgaa gccatgttcc tcctggagtt cttcctgccc 600

ctgggcatca tcctgttctg ctcagccaga attatctgga gcctgcggca gagacaaatg 660

gaccggcatg ccaagatcaa gagagccatc accttcatca tggtggtggc catcgtcttt 720

gtcatctgct tccttcccag cgtggttgtg cggatccgca tcttctggct cctgcacact 780

tcgggcacgc agaattgtga agtgtaccgc tcggtggacc tggcgttctt tatcactctc 840

agcttcacct acatgaacag catgctggac cccgtggtgt actacttctc cagcccatcc 900

tttcccaact tcttctccac tttgatcaac cgctgcctcc agaggaagat gacaggtgag 960

ccagataata accgcagcac gagcgtcgag ctcacagggg accccaacaa aaccagaggc 1020

gctccagagg cgttaatggc caactccggt gagccatgga gcccctctta tctgggccca 1080

acctctcctt aa 1092

<210> 2
<211> 363

<212> PRT
<213> Homo sapien

<400> 2

Met Asn Arg His His Leu Gln Asp His Phe Leu Glu Ile Asp Lys Lys
1 5 10 15

Asn Cys Cys Val Phe Arg Asp Asp Phe Ile Val Lys Val Leu Pro Pro
20 25 30

Val Leu Gly Leu Glu Phe Ile Phe Gly Leu Leu Gly Asn Gly Leu Ala
35 40 45

Leu Trp Ile Phe Cys Phe His Leu Lys Ser Trp Lys Ser Ser Arg Ile
50 55 60

Phe Leu Phe Asn Leu Ala Val Ala Asp Phe Leu Leu Ile Ile Cys Leu
65 70 75 80

Pro Phe Leu Met Asp Asn Tyr Val Arg Arg Trp Asp Trp Lys Phe Gly
85 90 95

Asp Ile Pro Cys Arg Leu Met Leu Phe Met Leu Ala Met Asn Arg Gln
100 105 110

Gly Ser Ile Ile Phe Leu Thr Val Val Ala Val Asp Arg Tyr Phe Arg
115 120 125

Val Val His Pro His His Ala Leu Asn Lys Ile Ser Asn Arg Thr Ala
130 135 140

Ala Ile Ile Ser Cys Leu Leu Trp Gly Ile Thr Ile Gly Leu Thr Val
145 150 155 160

His Leu Leu Lys Lys Lys Met Pro Ile Gln Asn Gly Gly Ala Asn Leu
165 170 175

Cys Ser Ser Phe Ser Ile Cys His Thr Phe Gln Trp His Glu Ala Met
180 185 190

Phe Leu Leu Glu Phe Phe Leu Pro Leu Gly Ile Ile Leu Phe Cys Ser
195 200 205

Ala Arg Ile Ile Trp Ser Leu Arg Gln Arg Gln Met Asp Arg His Ala
210 215 220

Lys Ile Lys Arg Ala Ile Thr Phe Ile Met Val Val Ala Ile Val Phe
225 230 235 240

Val Ile Cys Phe Leu Pro Ser Val Val Val Arg Ile Arg Ile Phe Trp
245 250 255

Leu Leu His Thr Ser Gly Thr Gln Asn Cys Glu Val Tyr Arg Ser Val
260 265 270

Asp Leu Ala Phe Phe Ile Thr Leu Ser Phe Thr Tyr Met Asn Ser Met
275 280 285

Leu Asp Pro Val Val Tyr Tyr Phe Ser Ser Pro Ser Phe Pro Asn Phe
290 295 300

Phe Ser Thr Leu Ile Asn Arg Cys Leu Gln Arg Lys Met Thr Gly Glu
305 310 315 320

Pro Asp Asn Asn Arg Ser Thr Ser Val Glu Leu Thr Gly Asp Pro Asn
325 330 335

Lys Thr Arg Gly Ala Pro Glu Ala Leu Met Ala Asn Ser Gly Glu Pro
340 345 350

Trp Ser Pro Ser Tyr Leu Gly Pro Thr Ser Pro
355 360

<210> 3
<211> 22
<212> DNA
<213> Artificial

<220>
<223> Novel Sequence

<400> 3
gctggagcat tcactaggcg ag 22

<210> 4
<211> 24
<212> DNA
<213> Artificial

<220>
<223> Novel Sequence

<400> 4
agatcctggt tcttggtgac aatg 24

<210> 5
<211> 1083
<212> DNA
<213> Mouse

<400> 5
atgagcaagt cagaccattt tctagtgata aacggcaaga actgctgtgt gttccgagat 60

gaaaacatcg ccaaggtctt gccaccggtg ttggggctgg aatttgtgtt cggactcctg 120

ggcaatggcc ttgccttgtg gattttctgt ttccacctca agtcctggaa atccagccgg 180

attttcttgt tcaacttggc cgtggctgac tttctcctga tcatctgcct gccgttcctg 240

acggacaact atgtccataa ctgggactgg aggttcggag gcatcccttg ccgtgtgatg 300

ctcttcatgt tggctatgaa ccgacagggc agcatcatct tcctcaccgt ggtggctgtg 360

gaccgctact tccgggtggt ccatccacac cacttcttga acaagatctc caaccggacg 420

gcggccatca tttcttgctt cttgtggggt ctcaccatcg gcctgactgt ccacctcctc 480

tatacaaaca tgatgaccaa aaatggcgag gcatatctgt gtagcagctt cagcatctgt 540

tacaacttca ggtggcacga tgctatgttc ctcttggaat tcttcttgcc cctggccatc 600

atcttgttct gctcaggcag gatcatctgg agcctgaggc agagacagat ggacagacat 660

gccaagatca agagggccat caacttcatc atggtggtgg ctattgtatt catcatttgc 720

ttcctaccca gtgtggctgt gcgcatccgc atcttctggc ttctctacaa atataacgta 780

cgcaactgtg acatctactc ctcggtggac ctggctttct ttaccaccct tagctttacc 840

tacatgaaca gcatgctgga ccctgtggtc tactatttct ccagcccatc tttccccaac 900

ttcttctcca cgtgtatcaa ccgctgcctt cgaaagaaaa cattgggtga acccgataat 960

aaccgaagca ctagtgtgga gctcacgggg gaccccagca caaccagaag tattccaggg 1020

gcgctaatgg ctgaccccag tgagccaggc agcccccctt atctggcttc cacatctcgt 1080

taa 1083

<210> 6
<211> 360
<212> PRT
<213> Mouse

<400> 6

Met Ser Lys Ser Asp His Phe Leu Val Ile Asn Gly Lys Asn Cys Cys
1 5 10 15

Val Phe Arg Asp Glu Asn Ile Ala Lys Val Leu Pro Pro Val Leu Gly
20 25 30

Leu Glu Phe Val Phe Gly Leu Leu Gly Asn Gly Leu Ala Leu Trp Ile
35 40 45

Phe Cys Phe His Leu Lys Ser Trp Lys Ser Ser Arg Ile Phe Leu Phe
50 55 60

Asn Leu Ala Val Ala Asp Phe Leu Leu Ile Ile Cys Leu Pro Phe Leu
65 70 75 80

Thr Asp Asn Tyr Val His Asn Trp Asp Trp Arg Phe Gly Gly Ile Pro
85 90 95

Cys Arg Val Met Leu Phe Met Leu Ala Met Asn Arg Gln Gly Ser Ile
100 105 110

Ile Phe Leu Thr Val Val Ala Val Asp Arg Tyr Phe Arg Val Val His
115 120 125

Pro His His Phe Leu Asn Lys Ile Ser Asn Arg Thr Ala Ala Ile Ile
130 135 140

Ser Cys Phe Leu Trp Gly Leu Thr Ile Gly Leu Thr Val His Leu Leu
145 150 155 160

Tyr Thr Asn Met Met Thr Lys Asn Gly Glu Ala Tyr Leu Cys Ser Ser
165 170 175

Phe Ser Ile Cys Tyr Asn Phe Arg Trp His Asp Ala Met Phe Leu Leu
180 185 190

Glu Phe Phe Leu Pro Leu Ala Ile Ile Leu Phe Cys Ser Gly Arg Ile
195 200 205

Ile Trp Ser Leu Arg Gln Arg Gln Met Asp Arg His Ala Lys Ile Lys
210 215 220

Arg Ala Ile Asn Phe Ile Met Val Val Ala Ile Val Phe Ile Ile Cys
225 230 235 240

Phe Leu Pro Ser Val Ala Val Arg Ile Arg Ile Phe Trp Leu Leu Tyr
245 250 255

Lys Tyr Asn Val Arg Asn Cys Asp Ile Tyr Ser Ser Val Asp Leu Ala
260 265 270

Phe Phe Thr Thr Leu Ser Phe Thr Tyr Met Asn Ser Met Leu Asp Pro
275 280 285

Val Val Tyr Tyr Phe Ser Ser Pro Ser Phe Pro Asn Phe Phe Ser Thr
290 295 300

Cys Ile Asn Arg Cys Leu Arg Lys Lys Thr Leu Gly Glu Pro Asp Asn
305 310 315 320

Asn Arg Ser Thr Ser Val Glu Leu Thr Gly Asp Pro Ser Thr Thr Arg
325 330 335

Ser Ile Pro Gly Ala Leu Met Ala Asp Pro Ser Glu Pro Gly Ser Pro
340 345 350

Pro Tyr Leu Ala Ser Thr Ser Arg
355 360

<210> 7
<211> 1086
<212> DNA
<213> Rat

<400> 7
atgagcaagt cagaccattt tctagtgata aacggcaaga actgctgtgt gttccgagat 60

gaaaacatcg ccaaggtcct gccgccggtg ttggggctgg agtttgtgtt tggactcctg 120

ggtaatggcc ttgccttgtg gatcttctgt ttccatctca aatcctggaa atccagccgg 180

attttcttgt tcaacctggc cgtggctgac tttctcctga tcatttgctt gccgttcttg 240

acggacaact atgtccagaa ctgggactgg aggttcggga gcatcccctg ccgcgtgatg 300

ctcttcatgt tggccatgaa ccgacagggc agcatcatct tcctcacggt ggtggctgtg 360

gacaggtact tcagggtggt ccacccgcac cacttcctga acaagatctc caaccggacg 420

gcggccatca tctcttgctt cctgtggggc atcaccatcg ggcctggaca gtccaccttc 480

ctctacacgg acatgatgac ccgaaacggc gatgcaaacc tgtgcagcag ttttagcatc 540

tgctacactt tcaggtggca cgatgcaatg ttcctcttgg aattcttcct gcccctgggc 600

atcatcctgt tctgctctgg caggatcatt tggagcctaa ggcagagaca gatggacagg 660

cacgtcaaga tcaagagggc catcaacttc atcatggtgg ttgccattgt gtttgtcatc 720

tgcttcctgc ccagtgtggc cgtgaggatc cgcatcttct ggctcctcta caaacacaac 780

gtgaggaact gtgacatcta ctcctctgtg gacttggcct tcttcaccac ccttagcttt 840

acctacatga acagcatgct cgacccggtg gtctactatt tctccagccc atctttcccc 900

aacttcttct ccacgtgcat caaccgttgc cttcgaagga aaaccttggg cgaaccagat 960

aataaccgga gcacgagtgt ggagctcacg ggggacccca gcacaatcag aagtattcca 1020

ggggcattaa tgactgaccc cagtgagcca ggcagccccc cttatctggc ttccacatct 1080

cgttaa 1086

<210> 8
<211> 361
<212> PRT
<213> Rat

<400> 8

Met Ser Lys Ser Asp His Phe Leu Val Ile Asn Gly Lys Asn Cys Cys
1 5 10 15

Val Phe Arg Asp Glu Asn Ile Ala Lys Val Leu Pro Pro Val Leu Gly
20 25 30

Leu Glu Phe Val Phe Gly Leu Leu Gly Asn Gly Leu Ala Leu Trp Ile
35 40 45

Phe Cys Phe His Leu Lys Ser Trp Lys Ser Ser Arg Ile Phe Leu Phe
50 55 60

Asn Leu Ala Val Ala Asp Phe Leu Leu Ile Ile Cys Leu Pro Phe Leu
65 70 75 80

Thr Asp Asn Tyr Val Gln Asn Trp Asp Trp Arg Phe Gly Ser Ile Pro
85 90 95

```
Cys Arg Val Met Leu Phe Met Leu Ala Met Asn Arg Gln Gly Ser Ile
            100                 105                 110

Ile Phe Leu Thr Val Val Ala Val Asp Arg Tyr Phe Arg Val Val His
        115                 120                 125

Pro His His Phe Leu Asn Lys Ile Ser Asn Arg Thr Ala Ala Ile Ile
    130                 135                 140

Ser Cys Phe Leu Trp Gly Ile Thr Ile Gly Pro Gly Gln Ser Thr Phe
145                 150                 155                 160

Leu Tyr Thr Asp Met Met Thr Arg Asn Gly Asp Ala Asn Leu Cys Ser
                165                 170                 175

Ser Phe Ser Ile Cys Tyr Thr Phe Arg Trp His Asp Ala Met Phe Leu
            180                 185                 190

Leu Glu Phe Phe Leu Pro Leu Gly Ile Ile Leu Phe Cys Ser Gly Arg
        195                 200                 205

Ile Ile Trp Ser Leu Arg Gln Arg Gln Met Asp Arg His Val Lys Ile
    210                 215                 220

Lys Arg Ala Ile Asn Phe Ile Met Val Val Ala Ile Val Phe Val Ile
225                 230                 235                 240

Cys Phe Leu Pro Ser Val Ala Val Arg Ile Arg Ile Phe Trp Leu Leu
                245                 250                 255

Tyr Lys His Asn Val Arg Asn Cys Asp Ile Tyr Ser Ser Val Asp Leu
            260                 265                 270

Ala Phe Phe Thr Thr Leu Ser Phe Thr Tyr Met Asn Ser Met Leu Asp
        275                 280                 285

Pro Val Val Tyr Tyr Phe Ser Ser Pro Ser Phe Pro Asn Phe Phe Ser
    290                 295                 300

Thr Cys Ile Asn Arg Cys Leu Arg Arg Lys Thr Leu Gly Glu Pro Asp
305                 310                 315                 320

Asn Asn Arg Ser Thr Ser Val Glu Leu Thr Gly Asp Pro Ser Thr Ile
                325                 330                 335

Arg Ser Ile Pro Gly Ala Leu Met Thr Asp Pro Ser Glu Pro Gly Ser
            340                 345                 350

Pro Pro Tyr Leu Ala Ser Thr Ser Arg
        355                 360
```

<210> 9
<211> 30
<212> DNA
<213> Artificial

<220>
<223> Novel Sequence

<400> 9
atgagcaagt cagaccattt tctagtgata 30

<210> 10
<211> 25
<212> DNA
<213> Artificial

<220>
<223> Novel Sequence

<400> 10
ttatctggct tccacatctc gttaa 25

<210> 11
<211> 30
<212> DNA
<213> Artificial

<220>
<223> Novel Sequence

<400> 11
atgagcaagt cagaccattt tctagtgata 30

<210> 12
<211> 25
<212> DNA
<213> Artificial

<220>
<223> Novel Sequence

<400> 12
ttatctggct tccacatctc gttaa 25

<210> 13
<211> 27
<212> DNA
<213> Artificial

<220>
<223> Novel Sequence

<400> 13
ctgatggaca actatgtgag gcgttgg 27

<210> 14
<211> 27
<212> DNA
<213> Artificial

<220>
<223> Novel Sequence

<400> 14
gctgaagctg ctgcacaaat ttgcacc 27